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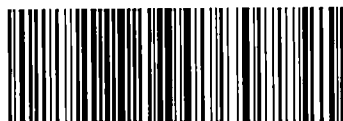
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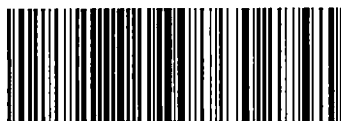
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Leading articles

Staging of oesophagogastric cancer

Until recently, detailed staging of solid tumours has received limited attention; the principal aim has been to exclude metastatic disease. In oesophageal and gastric cancer even this approach has been limited, and a significant number of patients has undergone unnecessary exploratory procedures to establish the inoperability of locally advanced disease. However, progress in primary medical management, with reproducible and durable response rates to chemotherapy, has encouraged the prospect of disease control and downstaging. Previously inoperable tumours may become operable and large studies, such as the Medical Research Council MAGIC (adjuvant gastric infusional chemotherapy) Trial, are currently assessing survival advantage.

Preoperative staging is necessary not only to identify patients with metastatic disease who require palliation, but also to identify those who are at high risk of early recurrence after radical curative resection (R_0). Experience from Japan and, more recently, Europe enables this latter group to be defined more predictably. All analyses of prognostic factors include nodal status as an independent prognostic variable, but this can be difficult to determine without the resected specimen. In practice, it is more feasible to try to determine tumour size and, by inference from histopathological databases, identify those at risk of nodal disease. T_1 tumours (mucosal or submucosal invasion) carry an 11 per cent risk of nodal disease (3 per cent to N_2 nodes), T_2 (muscularis propria or subserosal invasion) a 50 per cent risk (19 per cent to N_2 nodes), T_3 (serosal infiltration) a 74 per cent risk (39 per cent to N_2 nodes), and T_4 (invasion into adjacent organs) an 80 per cent risk (53 per cent to N_2 nodes)¹. Results of radical surgery (D_2 dissection) in selected series suggest 5-year survival rates of 85 and 55 per cent for stage I and II respectively, with an overall survival rate of 60 per cent; even patients with T_2N_2 (stage IIIA) cancers have approximately a 40 per cent survival rate^{2,3}. In randomized trials an advantage of D_2 over D_1 dissection has not been confirmed, but patients with earlier stage disease do have an overall longer survival^{4,5}.

Within the context of these surgical results patients with T_1 and T_2 tumours are less likely to relapse early than those with T_3 and T_4 tumours. Differentiation between these two groups would facilitate both the selection of appropriate treatment and the assessment of any benefit from neoadjuvant regimens. The principal problem in preoperative assessment has been the limited specificity and sensitivity of available imaging techniques in detecting tumour penetration, nodal involvement and metastatic dissemination. However, recent improvements in external imaging and the widespread use of laparoscopy have increased the accuracy of preoperative investigation. At the Second International Gastric Cancer Congress in Munich, Germany, April 1997, experience of the principal modalities was discussed in detail.

Although conventional computed tomography (CT) has been disappointing, modifications of technique to include contrast enhancement and the use of water as an intragastric contrast agent have been encouraging in the evaluation of T stage. Positioning the patient prone can improve examination of the lesser sac as the unattached posterior wall of the stomach falls away from the pancreas. The addition of helical scanning with faster scan times has provided some improvement, but overall experience suggests an increased accuracy only with T_3 and T_4 staging. Nodal staging is difficult because of the definition of criteria for nodal invasion, although most agree that a node measuring 8 mm or more is involved. The detection of metastatic spread to other organs is acceptably accurate for lesions larger than 1 cm, but miliary spread to the peritoneum or serosal surfaces is a major limitation. Results with magnetic resonance imaging have proved disappointing, principally because of image degradation by gastric wall motility. This may improve with faster scanners and better contrast media.

Although not strictly external imaging, endoluminal ultrasonography has become a significant and effective modality. It is limited by operator experience, but the assessment of T stage, particularly in the oesophagus, and of perioesophageal and

perigastric nodes has proven accurate. Sensitivities and specificities of 90 per cent or more have been reported for T stage⁶. While good quality images clearly show the layers of the oesophagus or stomach, problems are experienced with periserosal inflammation and/or infiltration which often occur with ulcerating lesions. This feature, together with anatomical differences in fat distribution between layers, may make differentiation between T₂ and T₃ difficult. However, overall, endoluminal ultrasonography is as good if not better than the best that CT can offer.

Laparoscopic staging is not new. However, improvements in laparoscopic technology have broadened its role. Simple inspection can identify peritoneal and serosal disease. The addition of cytology of peritoneal washings increases the identification of free tumour cells which correlate significantly with T₃ and T₄ disease. Laparoscopically assisted dissection has enabled retrogastric examination, which has hitherto been limited. Numerous authors have reported upstaging and downstaging in 40 per cent of cases⁷, with the prevention of exploratory laparotomy in up to 42 per cent⁸. The addition of contact ultrasonography has shown promising results, but in most series published to date it has not significantly altered the treatment decisions based on extended laparoscopy alone. Guided biopsy of lymph nodes, either at laparoscopy or during endoluminal ultrasonography, may improve nodal staging; the full impact of all these evolving approaches remains to be determined in large series.

A practical algorithm evolving from the above considerations is endoluminal ultrasonography after endoscopic and histological diagnosis. In the absence of serosal disease, proceed to radical surgery. In the presence of serosal infiltration, exclude metastatic spread by CT and laparoscopy, and consider neoadjuvant chemotherapy. In practice, treatment decisions will involve information from all modalities. A logical treatment philosophy should evolve not only for patients suitable for curative radical resection but also for those requiring palliation. Not all will necessarily require palliative surgery, with its attendant morbidity and mortality, as improvement in symptom control and performance status in those with advanced disease may be achieved by chemotherapy alone⁹. Finally, accurate staging should enable more meaningful results to be obtained from study of the management of advanced disease, and it should be possible to compare like with like between centres.

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Balanced analgesia: a prerequisite for optimal recovery

Treatment of postoperative pain is provided for humanitarian reasons and to reduce nociception-induced responses which may adversely influence organ function and contribute to morbidity¹. Despite tremendous progress in our understanding of pain physiology and increased attention from professional and government agencies, clinical surveys continue to indicate that routine pain treatment is unsatisfactory². The surgeon is often faced with questions of choice of analgesic treatment, risk of side-effects and degree of surveillance, and cost effectiveness. Although awareness and measurement of pain, education and increased use of simple, well established treatment regimens are the key factors in the general improvement of postoperative pain management², patients in severe pain with a high risk of adverse outcome may benefit from a more 'high-tech' analgesic programme. Such patients may also require increased attention to integrate pain relief into their postoperative rehabilitation.

The concept of balanced analgesia may be explained as follows. Optimal pain relief allowing normal function cannot be achieved by any single drug or method without major strains on equipment, surveillance systems or significant side-effects³. The rationale for multimodal or balanced analgesia is therefore to provide sufficient pain relief through additive or synergistic effects, using different analgesics, with a concomitant reduction of side-effects owing to the resulting lower doses of individual drugs and differences in side-effect profiles³.

Over the past decade many studies have supported the concept of balanced analgesia, with improved pain relief during cough and movement using epidural local anaesthetic–opioid regimens in major procedures^{1,3,4}, and opioid–non-steroidal anti-inflammatory drug (NSAID) combinations in minor or intermediate procedures^{3,5}. Concomitantly, data have demonstrated continuous epidural balanced analgesia to be safe following major surgery when provided in the surgical ward under the supervision of an acute pain service^{4,6}. Furthermore, NSAIDs, with or without opioids, are safe⁵, although their opioid-sparing benefits, leading to less sedation, nausea, vomiting, ileus and respiratory suppression, are less well established⁷.

Despite extensive data demonstrating the beneficial physiological effects of efficient analgesia, the effect on postoperative morbidity is still debatable¹. Analgesic therapy with opioids, systemically or by epidural, has only minor effects on the surgical stress response and organ dysfunction; this is also the case for NSAIDs^{1,8}. In contrast, central neural blockade with local anaesthetics (spinal or epidural analgesia) has a profound inhibitory effect on the catabolic stress response and improves cardiac pulmonary and gastrointestinal function. In addition, intraoperative blood loss and thromboembolic complications may be reduced in lower body procedures but, despite an associated improvement in pulmonary and cardiac function, such reduction of morbidity has not been a consistent finding in major (upper) abdominal and thoracic procedures^{1,4,8}. Neither has the well documented reduction in postoperative ileus by use of continuous epidural local anaesthetics or local anaesthetic–opioid combinations translated into a significant improvement in outcome, and hospital stay has not been reduced^{1,4,8}. These unexpected and disappointing findings may be explained by the lack of integration of effective analgesia with active rehabilitation⁸.

In the future, surgeons should be aware that balanced analgesia, either using low-cost combinations of conventional analgesics or a higher level of technology with epidural regimens, may improve pain relief. Balanced analgesia should, therefore, be used whenever reasonably possible. Low-dose epidural combination regimens after major surgery seem safe to use on surgical wards, but such treatment should be within the remit of an acute pain service with the assistance of appropriate anaesthetic expertise. Surgeons should be encouraged to increase their interprofessional collaboration, thereby enhancing progress and improvement in analgesia and postoperative outcome. Combinations involving paracetamol, α_2 -adrenergic agonists, newer slow-release long-acting local anaesthetics for

incisional use, ketamine and other drugs capable of reducing the postoperative neuroplastic response and increased pain sensitivity should be investigated. In addition, anti-inflammatory agents acting at the peripheral level (surgical site), such as new opioids, leukotriene inhibitors, glucocorticoids, substance P and bradykinin antagonists, need careful scrutiny. However, one of the most important future aspects for surgeons is an increased understanding of the pathophysiological role of pain and effective analgesia on postoperative morbidity. In this context it is essential to realize that single modality techniques or drug regimens cannot significantly reduce postoperative morbidity and mortality rates. On the other hand, multimodal intervention, with integration of effective analgesia in an enforced rehabilitation programme, may lead to a worthwhile reduction in postoperative morbidity, hospital stay and convalescence⁸.

In summary, postoperative pain relief continues to demand our awareness. All who care for postoperative patients should be fully aware of the benefits of balanced analgesia regimens. Increasing collaboration of surgeons with anaesthetists should support the establishment of acute pain services and subsequently integrate effective balanced analgesia into multimodal rehabilitation programmes. Such efforts may be expected to lead to improved quality of care for our patients, with less pain and reduced morbidity leading to cost efficiency⁸.

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Review

Spinal cord complications of thoracoabdominal aneurysm surgery

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Background Although rare, paralysis secondary to spinal cord ischaemia after aortic aneurysm surgery is a devastating complication. Many papers have been published on this topic but without a clear consensus on the best way of minimizing the problem. Recent articles have included advanced pharmacological approaches and the literature has been reviewed in light of these.

Methods Relevant papers were identified by an extensive text word search of the Medline database and a review of quoted articles.

Results Spinal cord complications are commoner after the repair of Crawford type II aneurysms than less extensive aneurysms. The presence of dissection, rupture and prolonged clamp times are associated with an increased incidence. About a quarter of all cord problems develop over 24 h after surgery and this may be due to a reperfusion type injury, although the exact mechanisms are by no means clear.

Conclusion A combination of rapid surgery, left heart bypass for the repair of more extensive aneurysms, free spinal drainage and the avoidance of postoperative hypoxia and hypotension help to minimize spinal cord ischaemia. No pharmacological agent has yet been shown conclusively to improve outcome in the clinical setting.

Since the first description of successful infrarenal aortic aneurysm repair by Dubost *et al.* in 1952¹ great advances have been made in aortic surgery. Infrarenal aortic aneurysms can now be repaired with acceptably low morbidity and mortality rates. However, more extensive aneurysms still remain a challenge and are associated with considerable mortality and morbidity rates because of ischaemic injury to the kidneys and viscera. One of the most feared and unpredictable complications is that of spinal cord dysfunction, a condition which is irreversible in the majority of cases. In this article the literature is reviewed with respect to the possible aetiologies of this condition and the strategies that have been adopted to prevent or reduce its incidence.

Blood supply of the spinal cord

The blood supply to the spinal cord is from spinal branches of vertebral, deep cervical, intercostal and lumbar arteries which, with the usually single anterior and double posterior spinal arteries, contribute to the formation of longitudinal anastomotic channels along the cord^{2,3}. Some blood supply may also reach the spinal cord from branches of the lateral sacral arteries arising from the internal iliac arteries⁴. Not all lumbar and intercostal arteries contribute equally to this anastomotic system and the degree of variability is considerable^{4,5}. The spinal cord branches of lumbar and intercostal arteries give rise to anterior and posterior radicular arteries which approach the cord along the ventral and dorsal nerve roots. Frequently one of these is larger than the rest and is termed the *arteria radicularis magna*⁵ also known as the artery of Adamkiewicz.

Traditional surgical anatomical teaching is that this main supply to the spinal cord is by two critical intercostal

or lumbar arteries usually arising at T12. However in humans variations are common and no specific level for the critical arteries can be relied upon. Indeed there often seems to be only one and in two-thirds of cases it arises on the left side⁷. In 85 per cent of cases it arises between T9 and L2, although it can arise as high as T5 or as low as L4⁶. What is clear, however, is that this artery may be responsible for the majority of the blood supply to the lower two-thirds of the cord, giving critical branches into both the anterior and posterior spinal cord arteries⁵; its interruption can cause paraplegia.

Incidence of spinal cord ischaemia during aortic surgery

The spinal cord, like the central nervous system as a whole, is an organ which is exquisitely sensitive to ischaemia. Complete ischaemia of less than 10 min can lead to infarction. While spinal cord infarction is a rare complication after infrarenal abdominal aneurysm surgery, it occurs with increasing frequency as more of the aorta is replaced. Most authors agree that the rate of paraplegia following infrarenal abdominal aortic aneurysm repair is in the order of 1 per cent or less^{7,8}. Because of this low rate there have been no studies specifically analysing factors which determine or predict its occurrence. Anecdotally it seems to be more common with ruptured aneurysm when, perhaps, hypotension plays a role. Similarly, it is well recognized as a complication of acute dissection of the aorta (without surgery), presumably due to 'stripping off' of the spinal arterial supply^{9,10}.

The association of spinal ischaemia and an aortic procedure was first recognized in 1667 by Stenon when he ligated the abdominal aorta of a rabbit, inducing paraplegia¹¹. The classical description of the anterior

spinal artery syndrome in association with resection of an abdominal aortic aneurysm, however, was not reported until 1962¹², fully 10 years after the first report of successful aneurysm repair¹. Perhaps this indicates the relative rarity of this complication, but anterior spinal artery syndrome is still the commonest neurological complication following infrarenal abdominal aortic aneurysm repair and almost all vascular surgeons will see at least one case during their career. Classically it consists of a flaccid lower limb paraplegia, dissociated sensory loss (absence of pain and temperature with intact proprioception and vibration sense) and sphincter incontinence. Complete recovery is unusual, but it may occur and is well described⁶. Presumably this is related to 'water-shed' areas of ischaemia without infarction.

It is in thoracoabdominal aneurysm (TAA) surgery that spinal cord problems are more often encountered as more of the lumbar and intercostal arterial supply is interrupted. This was recognized during the early development of this type of surgery^{13,14} and attempts were made to reimplant intercostal arteries where practicable. Crawford and co-workers were the first to report a large series of patients undergoing surgery for TAA. In 1980¹⁵ they described 138 procedures for TAA (including dissecting and syphilitic aneurysms) with an overall paraplegia rate of 9 per cent (12 of 138). In three patients the onset of the complication was delayed by 1–8 days and in four patients the deficit was mild and transient. Most cases occurred where the majority of the descending and abdominal aorta required replacement (ten of 47). The surgical technique used in this series included routine reattachment of one pair of intercostal arteries in an attempt to improve postoperative cord blood flow.

Crawford *et al.* later reported 605 patients¹⁶ of whom 6 per cent suffered paraplegia and 5 per cent suffered paraparesis. In atherosclerotic aneurysms involving most of the descending thoracic and abdominal aorta the rate of paraplegia and paraparesis combined was actually 21 per cent, and in similarly sited dissecting aneurysms it was 40 per cent. One of the risk factors identified was the extent of aneurysm. Using Crawford's classification, type II aneurysms (requiring the entire descending aorta to be replaced) carried the highest risk. Type I repairs (only the upper intrathoracic portion of the descending aorta replaced) carried a lower risk, as did type III aneurysms (only the lower part of the thoracic aorta replaced). Type IV aneurysms in which the repair is essentially below the level of the diaphragm were associated with the least risk. Crawford also stated that there was no statistical benefit from intercostal reimplantation. Hollier *et al.*¹⁷ also reported a series of 101 patients with non-dissecting TAAs with an overall mortality rate of 15 per cent and a paraplegia rate of 5 per cent; all cases of paraplegia occurred in type I or II repairs and 80 per cent of these patients had had intercostal arteries reimplanted. For type I or II TAAs paraplegia occurred in ten of 55 patients (18 per cent). In this series bypass techniques were not used routinely but intercostals were reimplanted where practicable. In the second part of the series improved management schemes (but no shunts or bypass) resulted in a significant fall in mortality rate to 2 per cent but the paraplegia rate remained unchanged. In a retrospective review from the authors' institution¹⁸ the rates for paraplegia were: type I, one of 20; type II, three of 39 for elective and three of ten for ruptured or emergency; type III, one of 18; and type IV, none of 63. Cox *et al.*¹⁹ likewise reported a paraplegia rate of 38 per cent when all

or most of the thoracic aorta was replaced (Crawford types I and II) and 12 per cent when only the lower aorta was replaced (Crawford types III and IV). More recently, certain groups have examined other methods of reducing spinal cord ischaemia. Drugs, cerebrospinal fluid (CSF) drainage, cooling and shunts have all been investigated, as well as methods for identifying and conserving critical intercostal arteries. Some of these regimens have been used clinically.

Animal models

Because of the problems of accumulating meaningful data from clinical studies involving an uncommon procedure, much work has been carried out using animal models. Most studies rely on variants of the Tarlov scale for grading neurological function after clamping of the aorta²⁰: grade I, no function; grade II, movement of joints perceptible; grade III, active movement of joints but unable to stand; grade IV, able to stand but unable to walk; and grade V, complete recovery.

Dogs and pigs²¹ have been used extensively but one of the most interesting models involves the New Zealand white rabbit^{22–25} in which a snare occlusion device is placed around the infrarenal aorta and tunnelled into a subcutaneous position. Following the animal's recovery from the procedure the snare can be tightened with the animal awake. Infrarenal clamping can induce ischaemic paraplegia in the rabbit and this model allows neurological effects to be observed in isolation from the confounding factors which are typical of most other models. After time intervals the snare can be released and any recovery observed. Ease of study is one of the great attractions of the method.

Aetiological factors

Ischaemia of spinal cord neuronal tissue causes a number of pathological changes. About two-thirds of the energy expended by central nervous system tissue is used to maintain cell function, i.e. maintenance of the ionic gradient across the cell membrane and synthesis of neurotransmitter substances. The other third is used for cellular homoeostasis²⁶. When the metabolic demands exceed the supply of oxygen and glucose the membrane gradient is quickly lost, with an influx of sodium and calcium ions and a loss of potassium ions leading to cell death. Cells that become ischaemic may recover if the membrane remains functional long enough for the supply of oxygen to be returned. In addition, ischaemic cells are known to release excessive amounts of excitatory amino acids including aspartate and glutamate^{27,28}. These bind to receptors including kainate, quisqualate and *N*-methyl-D-aspartate (NMDA) receptors which are widespread in the spinal cord. The former two open a monovalent sodium ion–potassium ion channel and the latter a non-selective divalent and monovalent channel that allows the free passage of sodium and calcium ions, further endangering the ionic gradient.

If an artery critical to the cord's blood supply is below the clamp and is then divided, some neural ischaemia will result. If this artery is reperfused there may still be a

postoperative insult. Cross-clamping time during the operation has been cited in a number of papers^{16,29} as a factor affecting neurological outcome. Experimentally, double occlusion of the aorta in dogs produces ischaemia in 90–100 per cent of cases after 45 min³⁰. Moore and Hollier²⁵ showed in rabbits that occlusion of the aorta caused paralysis in all animals after 2 min. Restoration of blood flow within 16 min guaranteed recovery, but after 27 min the paralysis was permanent. de Mol *et al.*³¹ reported 61 patients undergoing TAA repair by cross-clamping without adjuncts. Spinal cord injury occurred in eight patients, five suffered paraplegia and five recovered from paraparesis within 6 months. Risk factors in univariate analysis were the presence of symptoms and an emergency operation but cross-clamp time, aneurysm aetiology and the number of open intercostal arteries were not single factors associated with spinal cord injury. Crawford *et al.*¹⁶ in their review identified aortic dissection, rupture and postoperative bleeding as the most important aetiological factors for spinal cord complications. They also included cross-clamp time as significant, commenting that the important factor was probably whether collateral circulation to the cord has had time to develop^{15,16}. It is likely that this is the reason why acute dissection carries a high rate of spinal cord ischaemia (14–40 per cent); in purely atherosclerotic TAA on the other hand the intercostals are lost gradually because of aneurysm thrombus. Similar reasoning explains why cord complications are less common when only the descending thoracic aorta is replaced rather than the complete thoracoabdominal segment³².

One of the most intriguing features of the phenomenon of spinal cord dysfunction following major aneurysm surgery is that it does not always occur immediately; indeed 25 per cent of patients in Crawford and Schuessler's large series¹⁵ developed a delayed onset of paraparesis or paraplegia after an interval of up to 8 days. Others have also reported this phenomenon³³. That such patients were unimpaired initially effectively rules out mechanical interruption of the cord blood supply at the time of surgery as the major cause. There are also reported cases of reversible neurological deficit following TAA repair; Hill *et al.*³⁴ described two cases of paraplegia which resolved after the institution of CSF drainage. Crawford himself was first to highlight this phenomenon³⁵ and he suggested that postoperative hypotension and hypoxia, perhaps in a cord with some degree of existing ischaemia, were the precipitating causes. Other causes of delayed complications include thrombosis of a reimplanted critical artery, embolization, or reperfusion injury causing cord swelling and vasoconstriction with subsequent further ischaemia. Barone *et al.*³⁶ found a strong relationship between the severity of postischaemic spinal cord hyperaemia and the incidence of paraplegia in dogs. While there is no reported direct evidence that thrombosis or embolization are common causes of delayed spinal ischaemia, there is good evidence from animal models that reperfusion injury and secondary ischaemia can occur³³.

On removal of the aortic clamps the arrival of oxygen at the spinal cord creates a wave of free radical production thought to come from the reaction between increased concentrations of xanthine oxidase and low-energy phosphate compounds³⁷. The superoxide radical is produced first and this can initiate a cascade including the formation of the hydroxyl free radical via an iron- or copper-dependent (Haber–Weiss) reaction³⁸. This

increased production may overwhelm the capability of cells to scavenge these highly reactive species before they react with cellular structures, commonly the membrane lipids, initiating cytokine production and the release of arachadonic acid metabolites^{39,40}. It has been suggested that these oxygen-derived free radicals (ODFRs) play a significant role in the clinical morbidity associated with operations for TAA⁴¹ and that this may be due to a direct action, as they have been shown to damage glial cells⁴⁰, or a secondary event from either cord oedema within the confines of the spinal canal or decreased postreperfusion blood flow in ischaemic segments⁴². The latter may be mediated by vasoconstriction from endothelium-derived factors such as endothelin and thromboxane⁴³. Neutrophil activation is also enhanced following reperfusion injury⁴⁴ and direct injury from neutrophil-derived radicals may also play a part in delayed neuronal effects.

Intraoperative monitoring

It would be useful to have an intraoperative method of monitoring the spinal cord to detect the development of early ischaemia. Much has been written on the use of somatosensory spinal cord evoked potentials (SEPs) to fulfil this role, both in experimental studies^{45–47} and clinical surgery^{48–63}. The basis of the method used by most authors is stimulation of lower limb nerves while SEPs are recorded at the spinal and cortical levels. As ischaemia occurs, SEPs become diminished or absent^{45,50}.

Crawford *et al.*⁵⁹ described temporary distal aortic perfusion and SEP monitoring in 198 patients undergoing descending thoracic aneurysm or TAA repair. Pressures above 60 mmHg were achieved in only 50 per cent, but there was no significant difference in spinal cord complications between those with pressures above and those with pressures below 60 mmHg. The incidence of false-negative (13 per cent) and false-positive (67 per cent) SEPs was also deemed by the authors to render this technique unhelpful. Other authors have also reported misleading results from the technique^{54,60}, and there may be problems relating to SEPs and the effect that anaesthetic drugs may have on the latency and amplitude of potentials recorded^{61,62}.

Others have modified the technique in an effort to improve specificity. Drenger *et al.*⁶³ used direct spinal cord stimulation via an epidural electrode with monitoring over the cortex and claimed more accurate results. Similarly Yamamoto *et al.*⁵⁴ measured descending potentials in the thoracic and lumbar enlargements after direct cervical cord stimulation in 22 clinical cases. Abnormalities were correctly identified in the two patients who developed paraplegia. Although monitoring alone is of interest, it would obviously be of more value if it led to an alteration of surgical strategy to improve results⁵⁵. Shiya *et al.*⁵⁶ reported 20 patients in whom arteries were reconstructed if SEPs changed when a segment was clamped while femoro–femoral bypass was running. However, five patients still became paraplegic. Grossi *et al.*⁵⁷ measured SEPs and distal aortic pressures in dogs with a heparin-bonded venoarterial bypass; if distal pressure was kept above 60 mmHg SEPs readings remained normal and this correlated well with the incidence of complications. Although widely investigated, the precise value of this technique outside experimental studies still remains to be established.

Cerebrospinal fluid drainage

The spinal cord perfusion pressure (SCPP) depends on the difference between blood pressure and the CSF pressure. Thus either lowering CSF pressure or raising blood pressure will improve SCPP^{64,65}. That this might help prevent paraplegia due to aortic clamping was first reported in dogs by Miyamoto *et al.*⁶⁶. McCullough *et al.*⁶⁷ also used dogs to confirm that CSF fluid drainage could effectively improve SCPP and prevent neurological complications after descending aortic cross-clamping. Grubbs *et al.*⁴⁵ studied the relationship between CSF drainage during aortic cross-clamping and SCPP and SEPs in a canine model. Drainage of CSF had no effect on distal aortic pressure but significantly increased SCPP (from 9.4 to 21.8 mmHg) and decreased postoperative neurological injury.

As a result of these studies, the method was introduced into clinical practice by McCullough *et al.*⁶⁷, aiming to keep CSF pressure at less than 15 mmHg during the operation and for several days thereafter. Although Crawford *et al.*⁶⁸ had previously failed to show any benefit of CSF drainage in a prospective randomized study, they only removed CSF to a maximum of 50 ml and did not strictly maintain a constant pressure. Subsequently Safi *et al.*⁶⁹ compared 45 patients undergoing TAA repair with the previous 112 patients in the same institution. All 45 had CSF drainage and distal aortic perfusion with a paraplegia rate of 9 per cent compared with 31 per cent in the historical controls, thereby endorsing the technique. Others have described similar results⁷⁰ and there have also been reports of CSF drainage leading to resolution of paraplegia³⁴. It therefore appears to be a useful technique.

Preoperative localization of critical arteries

Preoperative radiological localization of the critical arteries to the spinal cord has been proposed as useful^{71,72} but the technique is difficult and has some risk. Preoperative identification of the cord's blood supply has been attempted using careful angiography performed in several planes. Difficulties include the aneurysm image overlying the origins of these arteries making visualization difficult. In addition it must be remembered that there is some risk of embolization from angiography.

Williams *et al.*⁷³ reported 47 patients who underwent selective catheterization of middle and lower thoracic intercostal arteries to identify the origin of the artery of Adamkiewicz. One patient had a significant athero-embolism and a second had transient lower extremity paraesthesia. No other complications occurred. What was less clear from this study, however, was how the knowledge gained improved outcome. The origin was found in only 26 patients, 21 of whom had surgery; eight of these 21 either died or suffered paraplegia whereas in the 19 patients operated on without identification of the critical artery five died or suffered paraplegia.

Kieffer *et al.*²⁹ studied 45 patients with preoperative selective angiography of intercostal and lumbar arteries. Identification of these arteries failed in five and was incomplete in a further nine. The dominant artery arose within the operated segment in 30 cases and attempts were made to reimplant it which were successful in 20. Spinal cord complications occurred in nine of the 45 patients but no complications occurred when the dominant spinal artery arose remote from the replaced

aorta. When it arose within the replaced segment the rate of spinal complications was 5 per cent (one of 20 patients) when revascularization was successful and 50 per cent (five of ten) when it was not. In the group in which the precise origin of the dominant spinal artery could not be determined the incidence of complications was 60 per cent (three of five). Cord complications were commoner when the artery of Adamkiewicz arose from an intercostal or lumbar artery obliterated at its origin but filled through collaterals or when the spinal cord blood supply was interrupted for more than 45 min.

The value of preoperative localization, therefore, seems to be in doubt. Rather than identify intercostals before surgery, most groups have practised a policy of selective reimplantation of the intercostal arteries identified as patent and important by their backbleeding at time of surgery.

Intraoperative localization of critical arteries

Intraoperative localization and preservation of critical arteries is a logical approach to avoiding cord ischaemia. The only clinically tested technique for intraoperative localization of spinal cord arterial supply was described by Svenson *et al.*⁷⁴. They cross-clamped the aorta segmentally, at three levels in the thorax and at two levels in the abdomen. Each segment was then injected with a hydrogen-saturated saline solution and the hydrogen-induced current impulse was then measured by a platinum electrode inserted in the dural space. Intercostal and spinal arteries from the segment with the strongest response were then reimplanted. Although this technique may be accurate in localizing the aortic segment with a vital cord supply, it seems impractical and likely to increase the duration of total ischaemia.

Temporary bypass or shunts

Bypasses or shunts have the theoretical advantage of maintaining distal perfusion while the upper clamp is in position and the upper anastomosis is being constructed, thereby reducing distal, visceral and spinal cord ischaemia. The bypass can be positioned in a number of ways. One of the commonest is left atrial to femoral bypass, but other methods such as bypass from the aorta above the upper clamp to the femoral artery, or from the femoral vein to the femoral artery can be used. Some have used temporary construction of an axillofemoral bypass⁷⁵. Bypass allows a centrifugal pump to be used with the possibility of heat exchangers in the circuit and the ability to regulate flows and pressures. This technique is often employed with cooling and sometimes with circulatory arrest. The main disadvantage is the need to give heparin, although this can be overcome by using a passive heparin-bonded shunt (i.e. a Gott type shunt)^{75,76}, which does not require systemic heparinization and which may therefore result in less bleeding. Some groups have even used pumped bypass without systemic heparinization to avoid this problem⁷⁷. Another major advantage of a shunt or temporary bypass is that the afterload on the heart is reduced during aortic clamping, although this is less easy to adjust with a non-pumped bypass system. Disadvantages of shunts include the technical problems which may arise from cannulating diseased femoral or iliac arteries or the left atrium, and the risk of

embolization from the aneurysm sac thrombus during shunt perfusion, especially if sequential clamping is employed.

Crawford *et al.* in 1981⁷⁸ described 112 patients with aneurysms confined to the descending aorta; paraplegia occurred in only 1 per cent and the survival rate was 91 per cent. In this report the authors stated that in the previous 35 patients with similar aneurysms in whom bypasses or shunts had been used the mortality rate was 22 per cent and the paraplegia rate 6 per cent. The message that shunts conferred no benefit was repeated in a later publication⁷⁹ and endorsed by others who also found bleeding complications to be more common⁷⁹.

Only relatively recently has interest been rekindled in the potential protective use of bypass techniques and many groups are now again using them for extensive aneurysms. Verdant *et al.*⁷⁵ reported their experience with 173, and later 366⁷⁶, consecutive cases of descending thoracic aortic replacement with a heparin-bonded Gott shunt (Argyle) and no systemic heparinization. No spinal cord dysfunction occurred. More recently Coseli *et al.*⁸⁰, who have followed Crawford's work in Texas, reported an incidence of paraplegia of 1.5 per cent in a series of 198 TAA repairs. They adopted a left heart bypass technique, but also included intercostal artery reimplantation and hypothermia in their routine management.

Pharmacological agents

Many animal trials have focused on drug administration designed to confer a neuroprotective effect^{81–87}. Protection of the ionic gradient during ischaemia, exogenous ODFR scavengers and blockage of local vasoconstriction have been investigated, either in isolation or in conjunction with other measures. Unfortunately, the blood–brain barrier provides a significant obstacle to systemic drug administration. Intravenous infusions may not give very high CSF concentrations and intrathecal infusions can potentially increase CSF pressure and so increase ischaemia. Drug compounds investigated include the following.

Barbiturates

Barbiturates are known to reduce the central nervous system metabolic rate and were used in the early days of cardiac surgery. Thiopentone, ketamine and halothane were compared, with and without hypothermia, in a rabbit model²⁹. Only thiopentone gave any protection from immediate injury compared with controls, but all but one of 12 treated animals went on to develop a delayed deficit. Hypothermia was successful at preventing both immediate and delayed injury, irrespective of the drug given.

Steroids

Steroids remain the mainstay of treatment following many acute neurological events, notably to lower raised intracranial pressure. Their use has also been advocated following subarachnoid haemorrhage to reduce cerebral ischaemia after vasospasm^{88,89}. Koc *et al.*⁹⁰ have shown that steroids reduce lipid peroxidation in rats after spinal cord ischaemia. In 1984 Laschinger *et al.*⁸¹ used methylprednisolone in dogs subjected to 10 min of cross-clamping beyond the time of loss of SEPs. There was no difference in the measured reduction of blood flow

between the treated groups and an untreated group, although 67 per cent of untreated animals developed paraplegia compared with none of the treated animals. More recently, again in dogs, it has been demonstrated that a combination of steroids and spinal drainage gave a greater protective effect than either treatment alone⁸².

Ion channel blockers

NMDA controls a sodium ion–potassium ion channel which is normally blocked by extracellular magnesium in a voltage-dependent manner; this has been demonstrated *in vitro* and *in vivo*^{91,92}. Rokkas *et al.*⁸³ blocked the NMDA receptor in pigs with dextrophan, a non-competitive antagonist, during thoracic aorta cross-clamping for 60 min. In treated animals they demonstrated a preservation of SEPs; in normothermic controls the extracellular glutamate concentration increased threefold while it was reduced in the treatment group.

Simpson *et al.*⁸⁴ used intrathecal magnesium sulphate before double clamping of the aorta in dogs. No drainage was performed and a significant drop in the SCPP was noted compared with controls. All eight treated animals had no measurable neurological deficit compared with only one of eight control dogs. The authors suggested that magnesium may have other potentially beneficial effects beyond the downregulation of the NMDA receptor. It is a cerebral vasodilator which may reduce postischaemic vasospasm, and also has widespread functions in the synthesis and maintenance of cell membranes. Follis *et al.*⁸⁵ used either magnesium ions or MK-801, a NMDA blocker, to show a similarly improved long-term neurological outcome in Sprague rats. Other evidence that the blockage of ion channels protects against ischaemia comes from Breckwoldt *et al.*⁸⁶ who used intrathecal tetracaine, a local anaesthetic agent with membrane-stabilizing properties, in a rabbit model during 30 min of cross-clamping. This gave impressive results although with small numbers: six of seven were protected from paralysis compared with paralysis in all four controls. These numbers are, however, too small to be statistically significant.

Free radical scavengers

ODFRs have been implicated in the pathophysiology of reperfusion injury following cardiac and mesenteric ischaemia. Allopurinol is a xanthine oxidase inhibitor and desferrioxamine is an iron-chelating agent. Qayumi *et al.*²⁰ used both of these agents before aortic clamping in pigs for a period sufficient to produce neurological impairment in a control group; the treated group all recovered by 24 h. This suggests a significant role for ODFRs in overall recovery, but whether it improves the initial ischaemic insult is less clear.

Superoxide dismutase (SOD) is an enzyme involved in the synthesis of free radicals that also scavenges excess quantities of such radicals. Unfortunately it does not cross the blood brain barrier easily. Granke *et al.*⁴¹ augmented spinal drainage in mongrel dogs with an intravenous dose of a polyethylene glycol-conjugated SOD (PEG-SOD) to overcome this problem. No dog with spinal drainage alone had any initial neurological deficit, compared with two of six in a group receiving PEG-SOD alone. However, in the drainage only group two of five developed a delayed paralysis, whereas none in a group receiving drainage combined with PEG-SOD did. The numbers are too

small for statistical analysis but the authors suggest that the effect of the SOD may be dose dependent. The reduction in delayed-onset paralysis may mean that free radicals are more important in exacerbating an injury in borderline ischaemic tissue following reperfusion than in creating the initial insult.

Dimethylthiourea is a hydroxyl free radical scavenger that can cross the blood brain barrier. Wisselink *et al.*⁸⁷ used it in a rabbit model to investigate when a free radical scavenger is most effective and so derive when a free radical-induced injury is most marked. Three groups had a 21-min occlusion of the aorta while conscious. Ten animals were treated with dimethylurea before clamping and ten before reperfusion. A further group were treated before reperfusion after 30 min of aortic occlusion. Successful prevention of paraplegia was noted in those treated early. Treatment before reperfusion provided less early benefit and poorer late results, although these were still better than in the control or in the prolonged ischaemia group, all of whom were paraplegic by 5 h with no recovery. This was interpreted by the authors as showing a significant protective effect of dimethylurea in the ischaemic period as well as in the period after reperfusion. Its effects are not confined to free radical scavenging as it has also been shown to inhibit neutrophil-mediated injury which may be an important part of the delayed injury.

Vasodilators

Prostacyclin is a potent vasodilator of which Iloprost (Schering Health, Burgess Hill, UK) is a long-acting analogue, used in the treatment of Raynaud's disease and other vasospastic disorders. It is also used routinely in some organ preservation solutions for its beneficial effects on cell viability during hypoxic storage. Katircioglu *et al.*²³ demonstrated its neuroprotective effect when infused systematically in rabbits before aortic occlusion. The infusion was started before ischaemia, increased during clamping and then continued at the lower dose for 5 min after reperfusion. Four of six treated animals were neurologically normal with one weak and another paralysed; one control was weak and the other five were paralysed. A reduction in distal aortic pressure was noted in the control group suggesting a poorer SCPP, but this did not reach statistical significance. The beneficial action of prostacyclin may derive from its vasodilatory action, but it can also inactivate leucocytes^{93,94}. In this study the animals were observed only at 24 h and the CSF pressure was not measured so it is difficult to separate the effects of the two mechanisms.

Svensson *et al.*⁹⁵ have used intrathecal papaverine, another vasodilator, in 11 patients in conjunction with spinal drainage. They had previously shown this agent significantly to increase the spinal cord blood flow in baboons⁹⁶. In their clinical cases there were no neurological complications and no systemic side-effects from the papaverine; again the numbers were too small to draw any statistically meaningful conclusion.

Others

Adenosine is an agent that has been shown to protect ischaemic tissues and is routinely added to some organ preservation solutions. Its action is still poorly understood although possibilities include enhanced regeneration of the intracellular free radical scavenger glutathione, a

neural depressive action or local vasodilatation. It also blocks platelet adherence and inhibits white cell accumulation⁹⁷. Herold *et al.*⁹⁸ used an intrathecal infusion of adenosine with hypothermic saline to give total protection in rabbits following prolonged aortic occlusion.

Naloxone is a short-acting opioid antagonist which was advocated by Acher *et al.*⁹⁹ after it appeared to reverse the immediate postoperative neurological deficit in two patients. Using a low-dose infusion started before operation and continued for 48 h in combination with spinal cord drainage, they experienced only one episode of paraplegia in 49 consecutive patients, compared with 11 in 61 retrospective controls who had neither treatment. Naloxone has widespread actions on many receptors¹⁰⁰ and its exact action in this context is unclear. The numbers of patients treated are yet again too small for statistical comparison.

Anaesthetic agents, such as sodium nitroprusside and nitroglycerin, are used routinely to control the systemic hypertension proximal to the cross-clamp during aortic repair. The former has been shown to reduce the SCPP, which lowers spinal cord blood flow, although the relationship is non-linear^{101,102}. Simpson *et al.*¹⁰³ studied the use of isoflurane for intraoperative blood pressure regulation in dogs and found it significantly improved spinal cord perfusion and neurological outcome when compared with sodium nitroprusside, although the mechanism is unclear.

There is obviously a plethora of potentially beneficial drugs that have been investigated. Barbiturates may be useful but have not been widely studied. Ion channel blockers, adenosine, prostacyclin and ODFRs seem to have benefits in experimental models, but the most effective safe doses, the durations of administration and the possible side-effects in clinical practice are not yet known. Steroids, naloxone and papaverine have all been used clinically, but only the first of these in large numbers of patients. There are obvious concerns about using large doses of an immunosuppressive drug in surgical patients but a number of groups include some steroids in their routine protocols as part of a multimodal approach^{104,105}. Following the discovery of a spinal cord ischaemic injury it seems logical to offer dexamethasone (and spinal drainage if not already in place) to try to reduce any effect of cord swelling. Otherwise, there is as yet no consensus on the best pharmacological approach.

Hypothermia

During hypothermic conditions the metabolic rate decreases, with a reduced loss of intracellular adenosine 5'-triphosphate stores and earlier resolution of lactic acidosis. This protects the tissue involved from ischaemic damage and perhaps reduces reperfusion injury. The precise temperature required to maximize this protective effect, while minimizing related complications such as cardiac dysrhythmia and coagulopathy, is not well defined. In animal models various levels of hypothermia from 18 to 35°C have been shown to increase tolerance to spinal cord ischaemia¹⁰⁶⁻¹¹¹.

Profound hypothermia and cardiac arrest

Hypothermic circulatory arrest was used in the early days of open cardiac surgery and more recently reintroduced for surgery of the transverse aortic arch for which it is

now frequently employed¹¹². Profound hypothermia with circulatory arrest is an attractive technique because it allows a bloodless field, minimizes the amount of dissection, avoids aortic clamping and provides cardiac as well as visceral and spinal protection. Total body cooling to a temperature of 15–20°C has a clear neuroprotective effect, as demonstrated by its successful use in total circulatory arrest during aortic arch replacement. Problems, however, include cardiac effects and the possibility of cerebral damage. It is especially useful when the reconstructions required are likely to prove complex and therefore prolonged. Kieffer *et al.*¹¹³ used it on 15 of 87 descending thoracic aneurysms or TAAs operated on through a left thoracotomy over a 21-month period. Four of the 15 patients died and one patient developed a delayed paraplegia. Others have also proposed that it should be used for descending thoracic aneurysms and TAAs when reconstruction is likely to prove complex^{114–116}.

Moderate hypothermia

Moderate cooling may provide a degree of protection without some of the dangers of total circulatory arrest. It is usually combined with bypass when a heat exchanger in the bypass circuit permits rapid cooling followed by rewarming at the end of the procedure. Pokrovsky *et al.*¹¹⁷ used external cooling with a circulating mattress and no bypass or CSF drainage. Their patients were mostly young, with isolated thoracic aneurysms, and mean clamp time was 47 min. The paraplegia rate was only 4 per cent. Frank *et al.*¹¹⁸ used moderate hypothermia (30°C) and partial bypass while maintaining an intrinsic cardiac rhythm, as well as sequential segmental repair and CSF drainage. Only 18 patients were reported, none of whom suffered paraplegia. The only complication related to the hypothermia was atrial fibrillation which occurred in three patients, but this was amenable to treatment. Because of the multimodal approach in a relatively small number of patients, it is impossible to assess what benefit specifically accrued from the use of hypothermia. However, the authors state that before the use of these adjunctive measures their paraplegia rate was 30 per cent with a mortality rate of 25 per cent. Temperatures should be measured above and below the clamps¹¹⁸. Frank *et al.* also recommend that facilities to convert to full cardiopulmonary bypass should be available in case serious ventricular dysrhythmias occur (although this was not needed in their series). Hollier *et al.*¹⁰⁴ also used moderate hypothermia as part of a multimodal approach to preventing paraplegia and encountered no paraplegia in a series of 42 patients.

Local cooling of the spinal cord

This has theoretical advantages because lower cord temperatures can be achieved without the systemic cardiac complications of other methods; additives can also be included in the perfusion solution. Three routes for perfusion have been investigated.

Subarachnoid infusions. Berguer *et al.*¹¹⁹ prevented paraplegia in dogs subjected to double aortic cross-clamping for 45 min by cooling the cord to 15°C with an intrathecal cold electrolyte infusion. Both treatment and control groups had a significant increase in CSF pressure, with the rise greater in the treated dogs; however on

removal of the infusion apparatus the CSF pressure dropped in association with leakage of CSF at the needle sites. There was no normothermic control infusion. Salzano *et al.*¹²⁰ had similar results in pigs using saline infused through a laminectomy at T4 to give a cord temperature of less than 20°C during aortic cross-clamping. No complications occurred in seven of eight animals. Wisselink *et al.*¹²¹ also successfully prevented all complications with a continuous infusion through an L7 laminectomy into the subarachnoid space of dogs. Isotonic saline was used at 2°C while keeping the CSF pressure constant.

Epidural infusion. The epidural space is smaller and less well insulated from the systemic circulation but it is more accessible. Vanicky *et al.*¹²² perfused the epidural space of rabbits undergoing aortic occlusion with isotonic saline at 5°C to give a cord temperature of less than 15°C. All animals were normal neurologically at 48 h. Marsala *et al.*¹²³ used an epidural infusion in dogs. Experimental animals had their cord temperature lowered to a mean of 28.5°C with cold (5°C) saline. Seven of eight animals obtained a full neurological recovery with the last animal having a partial recovery, compared with the control group in which none recovered fully. Tabayashi *et al.*¹²⁴ used a similar model but with clamp times of 60 and 120 mins. Cold perfusion protected all but one of the 11 experimental animals compared with all but one of the five controls.

In clinical practice Davison *et al.*¹²⁵ administered iced saline at 4°C into the epidural space at the level of T11–12 of eight patients undergoing TAA repair. A thermistor in the subarachnoid space measured the local mean temperature and this was also used for CSF drainage. The mean temperature reached was 26.9°C and the mean CSF pressure increase was 23 mmHg. No neurological complication occurred in any patient. Although only five of the eight lesions were type I or II, these data nevertheless demonstrate the apparent safety of the technique.

Flushing of the isolated aortic segment. The other method that has been investigated is the flushing of cold solutions into the isolated aortic segment. Allen *et al.*¹⁰⁶ used heparinized saline at 4°C in rabbits to give a mean cord temperature of 22.8°C. A normothermic control and sham-operated control were also performed. A drop in core temperature was noted but this recovered within 60 min of reperfusion. One of the treated animals had a weak limb that had not improved after 24 h, while all the control animals had a flaccid paralysis at that time. Herold *et al.*⁹⁸ used cold saline at 8°C combined with adenosine in a bolus followed by an infusion to give a final estimated cord temperature of 25°C in rabbits undergoing 30 min of aortic occlusion. They had complete success at preventing paraplegia.

Fehrenbacher *et al.*¹⁰⁵ published their results of 23 consecutive type I and II TAA repairs, including seven patients with either an acute rupture or dissection. They employed segmental aortic repair combined with a cold (8–10°C) aortic electrolyte solution containing heparin, methylprednisolone and mannitol. The solution was infused under pressure into isolated portions of the aorta before segmental replacement, while the distal aorta was perfused via a left atrial–femoral bypass. An attempt was made to reimplant all intercostal arteries between T8 and

L2. Up to 2 l of the fluid was used and the core temperature kept above 35°C with an in-line heat exchanger. Only one patient became paraplegic. These results are impressive, although the multimodal approach renders the role of cooling unclear. In addition, neither the CSF temperature attained nor whether CSF drainage was employed was recorded.

Conclusions

Spinal cord ischaemia remains a major problem associated with the repair of extensive aortic aneurysms. The cause is probably multifactorial and a reduction in its incidence is likely to require an approach which takes this into account. From the present review it appears prudent to minimize clamp times with a mixture of rapid surgery and elective bypass for those cases predicted to require more than one distal anastomosis before reperfusion, or when extensive (type II) aneurysms are being repaired. CSF drainage is straightforward and, although much of the data are inconclusive, little is lost by using it for all aneurysms that extend above the diaphragm. Intraoperative and postoperative hypotension and hypoxia are also almost certainly exacerbating factors and should be guarded against with a rapid infuser and elective postoperative ventilation.

SEPs and preoperative or peroperative identification of critical intercostal arteries do not appear to be worthwhile on a routine basis; the problem of misleading or inadequate information is too great. It is difficult to know whether routine reimplantation of backbleeding intercostal arteries will significantly prevent paraplegia, but if this will not greatly prolong clamp time in patients not on bypass it seems reasonable.

Total hypothermic circulatory arrest has too high a complication rate to be recommended routinely. However, local epidural cooling of the cord is a convincing new intervention that may have a significant effect on clinical practice in the near future. The specific technique has been developed over a number of years in one particular unit and it may be difficult to reproduce elsewhere. Nevertheless, this method seems worthy of further investigation by any department in which extensive aortic procedures are done on a regular basis.

At present, despite extensive animal experiments, there is no pharmacological agent that has been shown convincingly to help in a clinical setting. Prospective clinical drug trials involving TAA repair will always be difficult because of the relative rarity of the condition. It may be that a different model of neuronal ischaemia, e.g. subarachnoid haemorrhage, could provide initial data on drug dosage and administration which could then be applied to TAA surgery.

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Magnetic resonance imaging in evaluation of the common bile duct

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Background The ideal method for evaluation of the common bile duct (CBD) before or during cholecystectomy remains controversial. Magnetic resonance cholangiography (MRC) is a new, promising technique. A prospective evaluation is reported.

Method Sixty-one patients (45 women) were studied by MRC. There were 29 patients with symptomatic gallstone disease and without clinical, biochemical or ultrasonographic evidence of CBD stones (group 1); 28 of them also underwent intraoperative cholangiography (IOC). In addition, there were 21 patients with symptomatic gallstone disease, with mild biochemical and ultrasonographic signs of CBD involvement (group 2), of whom 19 underwent IOC, and 11 patients with symptomatic CBD stones (group 3), nine of whom had preoperative endoscopic retrograde cholangiopancreatography (ERCP) following MRC.

Results MRC showed that no patient in group 1 and three patients in group 2 had CBD stones. Three patients (one in group 1, two in group 2) did not undergo IOC because of technical or clinical problems. In group 3, ERCP confirmed the results of MRC in nine patients. Two patients underwent open surgery because of ultrasonographic, MRC and radiographic signs of pancreatic malignancy.

Conclusion MRC could replace IOC and ERCP for identification of asymptomatic CBD stones. In symptomatic patients MRC combined with other non-invasive imaging techniques can direct the surgeon to appropriate management.

Laparoscopic cholecystectomy represents the 'gold standard' in the treatment of gallbladder stone disease. Since it is a minimally invasive technique, it may be important to obtain as much information as possible about the presence of stones in the common bile duct (CBD), because of the change in the therapeutic approach that might be needed. Magnetic resonance cholangiography (MRC) is a non-invasive diagnostic procedure for evaluation of the biliary tract. This imaging technique may be used in two-dimensional fast spin-echo (FSE) sequences with maximum intensity projection followed by three-dimensional reconstruction of the image¹ or directly in three-dimensional FSE sequences².

In the present study the effectiveness of MRC has been tested in 61 patients scheduled for laparoscopic cholecystectomy. The results have been verified by intraoperative cholangiography (IOC) and endoscopic retrograde cholangiopancreatography (ERCP). The aim of this work was to derive a valid preoperative diagnostic algorithm for patients undergoing laparoscopic cholecystectomy in the presence of suspected cholelithiasis.

Patients and methods

From April 1992 to December 1996, 166 patients (110 women; mean age 57.2 years) underwent laparoscopic cholecystectomy in this centre. A magnetic resonance imaging unit became available in the centre in September 1994. Starting from then, MRC was used in the preoperative study of 61 patients (45 women) scheduled for laparoscopic cholecystectomy. Mean age was 49.2

years. A GE Vectra 0.5-T scanner (General Electric, Milwaukee, Wisconsin, USA) was used in all patients. First an axial FSET2 of the upper abdomen was obtained in all patients. MRC was then performed using two-dimensional T2-weighted FSE sequences (TR (time repetition) 5–6000/TE (time echo) 160–180), matrix 160 × 224, factors 13 and FOV (field of view) 30–33 cm, and slice thickness 5 mm with no interslice gap. The images were obtained using a body coil with the patient in the supine position and using coronal plane acquisition. Neither intravenous nor oral contrast agents were administered. The total imaging time for MRC was about 5 min. These images were processed using a maximum intensity projection algorithm followed by a three-dimensional reconstruction of the image. Total magnet time, including patient positioning and scout imaging, was approximately 16–18 min.

The patients were grouped and studied as follows. group 1 comprised 29 patients with symptomatic gallbladder stones, without evidence of CBD stones by clinical (jaundice, pancreatitis), biochemical (raised serum bilirubin, alkaline phosphatase, glutamic-oxaloacetic transaminase, amylase or γ -glutamyl transferase levels) or ultrasonographic criteria; 28 of these patients underwent IOC. Group 2 comprised 21 patients with symptomatic gallbladder stones with no clinical but mild biochemical and/or ultrasonographic signs (CBD enlargement not exceeding 0.8 cm) of CBD stones; 19 of these patients underwent IOC. Group 3 comprised 11 patients with symptomatic CBD stones. All of them showed jaundice, and five complained of pancreatitis (before any endoscopic intervention). These patients had biochemical abnormalities and evident CBD enlargement on ultrasonography (range 0.8–1.5 cm) (Table 1); nine patients had preoperative ERCP following MRC.

Results

MRC showed no CBD stones in group 1. In group 2 (21 patients) three patients showed CBD stones on MRC.

Table 1 Ultrasonographic and laboratory data

	Group 1	Group 2	Group 3
CBD diameter on ultrasonography (cm)	0.5 (0.4–0.6)*	0.7 (0.6–0.8)	1.3 (0.8–1.5)
Serum bilirubin (mg/dl)	0.7 (0.1–1)†	2.9 (1–4)	7.8 (4–15)
Serum alkaline phosphatase (units/l)	85 (35–110)†	145 (110–150)	260 (150–400)
Serum γ -glutamyl transferase (units/l)	28 (1–35)†	150 (50–200)	250 (200–400)
Serum glutamic-oxaloacetic transaminase (units/l)	15 (1–40)†	120 (40–200)	310 (200–400)
Serum amylase (units/l)	25 (1–85)†	125 (85–150)	240 (150–300)
Patients with jaundice	0	0	11
Patients with pancreatitis	0	0	5

Values are mean (range). *Normal hospital range in patients with gallbladder *in situ*; †normal hospital range. CBD, common bile duct.

Two of them had CBD dilatation and one patient had intraductal abnormalities. Patients in both groups ($n = 50$) underwent laparoscopic cholecystectomy. IOC confirmed the results of MRC. Of those with abnormal MRC findings, two patients had a small stone impacted in the papilla and one had two small calculi 1 cm below the cystic duct confluence. One patient in group 1 and two patients in group 2 did not undergo IOC because of technical or clinical (inflammatory adhesions) problems. In group 3 (11 patients) five patients had CBD dilatation on MRC and four showed intraductal abnormalities. ERCP confirmed the findings. Three patients had a periampullary stone and six had multiple stones filling the CBD from the cystic duct confluence down to the papilla. All nine patients underwent laparoscopic cholecystectomy within 2 weeks following ERCP and sphincterotomy. The remaining two patients had ultrasonographic, MRC (the image was of biliary stricture) and radiographic signs of pancreatic malignancy, and underwent exploratory laparotomy followed by a palliative cholecystojejunostomy.

Discussion

Since laparoscopic cholecystectomy has become the preferred option for most surgeons, visualization of the CBD to detect suspected or unsuspected stones has become a major problem once more. A CBD evaluation is advisable in asymptomatic patients in whom a raised level of serum bilirubin, γ -glutamyl transferase, alkaline phosphatase or amylase is found alone or associated with enlargement of the CBD on ultrasonography, and in those with symptoms of CBD involvement (jaundice, pancreatitis)³.

However, between 1.2 and 12.4 per cent of all patients with gallbladder stones^{4,5} may have CBD calculi in the absence of any clinical, biochemical or radiological signs of choledocholithiasis. Various diagnostic approaches are currently used to study these patients. In symptomatic and asymptomatic patients with biochemical and/or ultrasonographic abnormalities, the present authors and most others perform preoperative ERCP to exclude CBD stones. If stones are detected a sphincterotomy followed by extraction of stones may be curative^{6,7}.

Some authors^{4,8–10} advocate IOC in uncertain or symptomatic cases. If stones are found, they are extracted by means of a choledochoscope while exploring the CBD, at the time of laparoscopic cholecystectomy. The presence of choledocholithiasis in these patients is uncertain enough to justify the continuous search for a way to select patients for preoperative diagnostic ERCP or IOC. The results, especially for asymptomatic patients, are controversial^{5,11–13}. Moreover, although direct cholangiograms

obtained with ERCP or IOC have an accuracy ranging from 92 to 98 per cent^{14,15}, cannulation of the papilla of Vater may not be achieved in 5–19 per cent of cases^{16,17}. Direct cholangiograms obtained by ERCP may produce immediate or delayed bleeding, cholangitis and pancreatitis^{18,19}, especially if sphincterotomy is performed. On the other hand, IOC performed during laparoscopic cholecystectomy may cause an injury to the CBD, when the latter is mistaken for the cystic duct and cannulated⁵. The incidence of false-positive cholangiograms ranges from 2 to 16 per cent^{15,20}. IOC normally lengthens the operative laparoscopic time and, because of technical or anatomical problems, may be unsuccessful in 5–45 per cent of cases^{4,21}.

The advantages provided by MRC compared with other imaging techniques can be summarized as follows. (1) It is a non-invasive way of studying the biliary tree without using ionizing radiation. (2) MRC does not require the administration of potentially dangerous contrast agents, which are needed when performing ERCP, percutaneous transhepatic cholangiography or computed tomography (CT) cholangiography²². (3) The sensitivity of MRC in detecting CBD stones or strictures may reach 95–100 per cent. MRC gives high-resolution projectional images not achievable with ultrasonography, CT or biliary scintigraphy, and its sensitivity for a diagnosis of CBD calculi is superior to that of ultrasonography or CT²². (4) A good high-resolution image of the pancreatic duct can be obtained at the same time²³. (5) MRC may distinguish non-invasively malignant from benign processes before operation²⁴, and directs the surgeon to appropriate management.

Pneumobilia, haematobilia, surgical clips or protein plugs may be the cause of false-positive findings at MRC, so caution is recommended in the interpretation of images²⁵. Nevertheless the introduction of MRC might change the approach to suspected choledocholithiasis in patients awaiting laparoscopic cholecystectomy. MRC may help in the decision to explore the CBD, saving the patient from invasive preoperative, intraoperative or post-operative diagnostic procedures. Although MRC cannot be proposed as a screening method for all patients awaiting laparoscopic cholecystectomy because of its high cost and the limited number of nuclear magnetic resonance units available, nevertheless in asymptomatic patients with biochemical or ultrasonographic signs of CBD involvement, or in symptomatic subjects (groups 2 and 3 in the present study), MRC should be performed before operation, as shown in the algorithm proposed in Fig. 1. Regardless of the preferred therapeutic approach to choledocholithiasis^{4–10}, MRC provides effective visualization of the CBD in selected groups of patients, separating in a clear way the diagnostic non-invasive preoperative

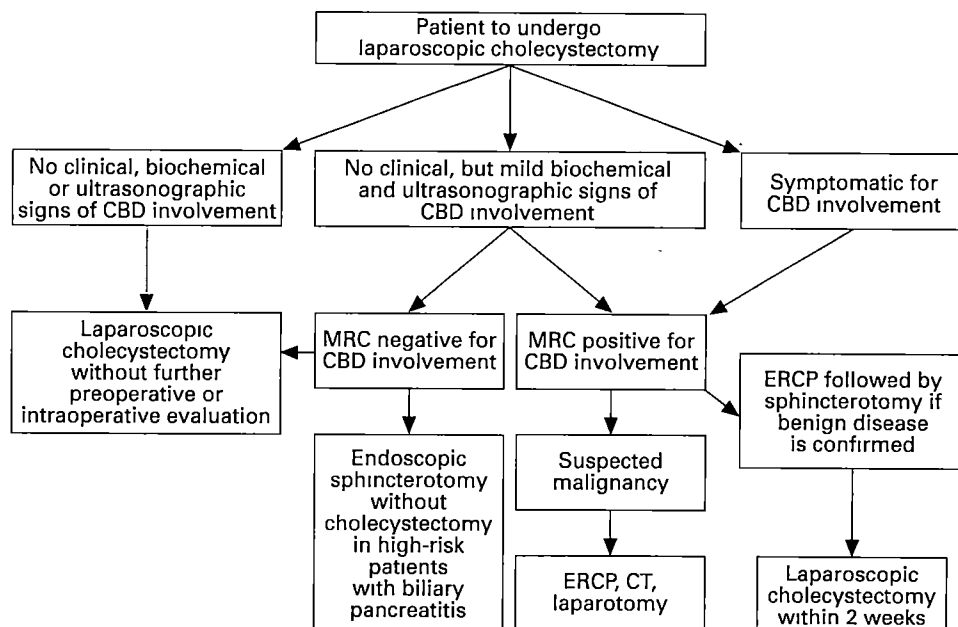


Fig. 1 Algorithm for preoperative diagnosis of choledocholithiasis. CBD, common bile duct; MRC, magnetic resonance cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography

time from the therapeutic one. The diagnostic need for ERCP or IOC may be reduced significantly by the correct use of MRC.

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Surgical workshop

Reliable double-component knots for laparoscopic surgery

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This report describes a quick and simple two-stage technique for tying laparoscopic square knots.

Surgical technique

The technique comprises an extracorporeal stage (Fig. 1, steps A-C) and an intracorporeal stage (Fig. 1, steps D-F). First, a

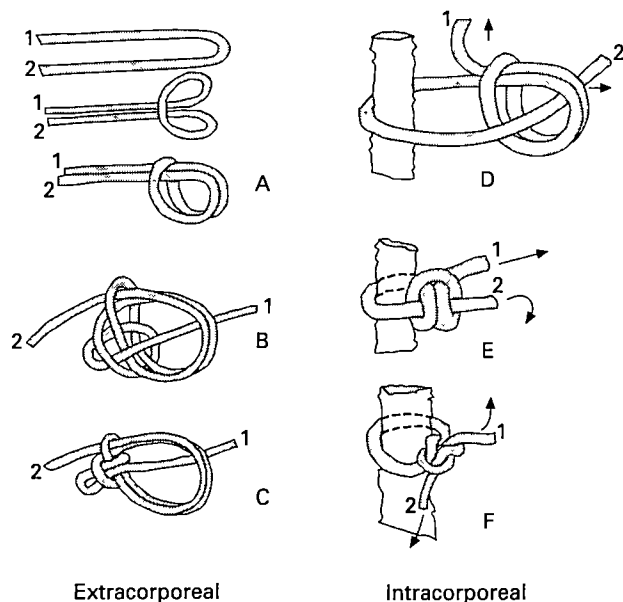


Fig. 1 Two-stage procedure for tying a square knot in laparoscopy

double loop is created by folding the bight back on itself (step A). This loop is secured with a false knot (steps B and C). The entire structure, held with forceps grasping the false knot, is then passed into the abdomen via a sheath. Having introduced the thread into the abdomen, and after passing tail 2 around the structure to be ligated or through the structures to be sutured, tail 2 is then passed through the double loop, the false knot is then undone by pulling on tail 1, giving rise to the knot shown in step D. Tail 2 is then tensioned in the vertical direction and tail 1 perpendicular to this (step D), sliding the knot up to the tissue and pulling it tight. Subsequently, the direction of tension is first reversed (tail 2 horizontally, tail 1 vertically; step E), then changed again (both tails horizontally, although in opposite directions; step F), transforming the original two-loop slip knot into a square knot.

This basic procedure can be modified in various ways. First, the number of loops created at step A may be increased to three or more. Second, the loops may be twisted or transposed; this creates an additional loop in the final knot. Third, the above two variations may be combined.

Discussion

Laparoscopic knots are often less secure than hand-tied knots^{1,2}. In both cases the most secure option is the flat square knot². The present procedure produces laparoscopic square knots. Similar two-stage procedures (namely the Dundee knot and the sliding knot for initiation of a continuous suture³) do not give rise to a square knot.

The technique is quick, as only the second stage is carried out during surgery, and versatile. Some of the variations give knots similar to those described by Delimar and Korzinek⁴ for open surgery.

The procedure can be used for ligating sectioned tubular structures, although it is especially useful for ligating non-sectioned tubular structures or for starting a continuous suture. Braided sutures should be used; monofilament sutures are not suitable because of the memory effect.

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Surgical strategies for carcinoma of the hepatic duct confluence

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Background This study was conducted to clarify the clinicopathological factors influencing appropriate surgical strategy and survival in patients with carcinoma of the hepatic duct confluence.

Methods A total of 66 patients who underwent local resection of the bile duct with ($n = 44$) and without ($n = 22$) hepatectomy were reviewed retrospectively.

Results Fifteen of the 44 patients who had hepatectomy and two of the 22 who did not suffered major postoperative complications ($P < 0.05$). As the pT category rose, the incidence of microscopic tumour extension increased significantly. Invasion at the surgical margins was more frequent in the patients who did not have hepatectomy than in those who did. Extramural tumour extension was found in 23 of 28 patients, and its prevalence was higher in the hepatic direction than the duodenal direction. Cancer invasion to the caudate lobe was found in nine of 21 patients. Thirty of 44 patients who underwent hepatectomy had a curative resection compared with six of 22 who did not have hepatectomy ($P < 0.01$). The cumulative survival rates after curative resection were significantly higher than after non-curative resection ($P < 0.01$).

Conclusion Hepatectomy with caudate lobectomy improves the curability and prognosis because these tumours frequently invade the surgical margins. However, operative morbidity is higher with this procedure.

More than 40 years have passed since the first report of resection for a carcinoma originating at the hepatic duct confluence by Brown and Mayers¹ in 1954, yet many questions regarding the management of this tumour are still controversial^{1–11}.

Despite the fact that carcinoma of the hepatic duct confluence is usually slow growing and is not associated with a high rate of distant metastasis, the diagnosis usually is not made until the bile duct is occluded and the patient is jaundiced^{10,12}. Even small tumours, because of their proximity, may infiltrate any or all of the following structures: the portal vein, the hepatic artery, and the parenchyma of the liver around the hepatic hilum, including the caudate lobe. Such infiltration may render curative excision technically difficult and often impossible^{7,8,10,11}.

Nevertheless, some studies^{5–7,13} have concluded that excision is the best form of treatment in terms of both length and quality of survival. Most of the controversy concerning excision to achieve a 'cure' surrounds the ability of local resection to completely remove all tumour and thus alter the natural history of the disease⁴. This is principally attributable to the tendency of the tumour to grow into the perineural tissue and spread for a considerable distance along the bile duct wall.

In some studies histological examination of resected specimens has demonstrated a positive correlation between the absence of residual tumour in the surgical margins and long-term survival^{8,11}. This has encouraged some authors to recommend a radical approach, including extensive liver resection and in some cases hepatectomy and transplantation^{9,10,14}. Others have stated that this suggests that the disease is multifocal and that performing hepatic resection in addition will not necessarily ensure that the surgical margins are free from tumour⁴. Moreover, if hepatic resection is associated with significant operative morbidity and mortality rates, it may not yield a significant overall benefit^{3,7}.

In this paper, experience with the surgical treatment of carcinoma of the hepatic duct confluence is reported, with emphasis on the operative procedures that allow potentially curative resection.

Patients and methods

Patients

Between September 1976 and August 1995, 87 patients with carcinoma of the hepatic duct confluence were admitted to this hospital. In 14 patients, obstructive jaundice was treated by percutaneous transhepatic biliary drainage (PTBD) alone, the other 73 patients were treated surgically. The surgically treated patients comprised 46 (63 per cent) men and 27 (37 per cent) women, with a mean age at the time of operation of 62.1 (range 36–89) years. Obstructive jaundice was present in 65 (89 per cent) of these 73 patients and PTBD was performed before operation in 63. Tumour resection was performed in 66 (90 per cent) of the 73 patients. The surgical procedures in the resected patients included resection of the extrahepatic bile duct plus hepatectomy in 44 (67 per cent) and resection of bile ducts alone in 22 (33 per cent) (Table 1).

Statistical analysis

Variables were compared using the χ^2 test or Student's *t* test. Survival curves were constructed using the product-limit method of Kaplan and Meier. Differences between the survival curves were analysed by the generalized Wilcoxon test, and a significant difference was defined as $P < 0.05$.

Results

Operative morbidity and mortality rates

Major postoperative complications occurred in 17 (26 per cent) of the 66 patients who underwent resection (Table 2). The most common complication was postoperative hepatic failure, which occurred in eight patients. The incidence of major complications was higher in the patients who had hepatectomy than in those who did not have hepatectomy ($P < 0.05$). The overall 30-day operative

Table 1 Surgical procedures in 66 resected patients

Surgical procedure	No. of patients	With caudate lobectomy
With hepatectomy	44	39
Left trisegmentectomy	1	1
Extended right lobectomy	10*	9
Extended left lobectomy	7†	7
Left lobectomy	13‡	12
Resection of S4a + S5	8‡	5
Caudate lobectomy alone	5§	5
Without hepatectomy	22	—
Local resection of extrahepatic bile ducts and hilar bile duct	22¶	—
Total	66	39

*Resection of the portal vein (three patients); †resection of the portal vein (one); ‡resection of the hepatic artery (one); §pancreatoduodenectomy (two); ¶pancreatoduodenectomy (three)

Table 2 Major postoperative complications in 66 resected patients

Major complications	No. of patients	With hepatectomy (n = 44)	Without hepatectomy (n = 22)
Hepatic failure	8	7	1
Leakage of biliary anastomosis	6	6	0
Multiple organ failure	3	3*	0
Respiratory failure	3	3	0
Renal failure	3	3	0
Upper gastrointestinal bleeding	3	3	0
Intra-abdominal bleeding	2	1	1
Disseminated intravascular coagulopathy	2	1	1
Fulminant hepatitis	1	1	0
Total	17	15 (34)	2 (9)†

Values in parentheses are percentages. *One patient died within 1 month after surgery. † $P < 0.05$ versus patients with hepatectomy (χ^2 test)

mortality rate of the patients who underwent resection was only 2 per cent. One patient, whose preoperative condition was complicated by severe cholangitis, died from multiple organ failure 14 days after right hepatic lobectomy with resection of the caudate lobe and portal vein.

Tumour involvement of the surgical margins

The surgical margins were examined histologically for cancer cell invasion. Cancer cells were present at the cut edge of the bile duct in the hepatic direction and the dissected margin of the tumour in the transverse plane in five and 11 patients, respectively of the 44 patients who underwent hepatectomy, but the cut edge of the bile duct in the duodenal direction was cancer free. Invasion of the surgical margins was significantly more common among the 22 patients without hepatectomy ($P < 0.01$ for all margins compared with the patients who had hepatectomy) (Table 3).

Table 3 Cancer invasion of the surgical margins

	No. of patients	Invasion of surgical margins		
		hw(+)	dw(+)	ew(+)
With hepatectomy	44	5	0	11
Without hepatectomy	22	11*	7*	15*
Total	66	16 (24)	7 (11)	26 (39)

Values in parentheses are percentages. hw(+), Presence of cancer cells on the cut edge of the bile duct in the hepatic direction; dw(+), presence of cancer cells on the cut edge of the bile duct in the duodenal direction; ew(+), presence of cancer cells on the dissected margin of the tumour in the transverse direction. * $P < 0.01$ versus patients with hepatectomy (χ^2 test)

Table 4 Microscopic tumour extension in 66 resected patients

Local extent of tumour*	No. of patients	Lymph node metastasis positive	Lymphatic permeation positive	Venous invasion positive	Perineural infiltration positive
pT ₁	4	0	0	0	0
pT ₂	27	7	20	10	15
pT ₃	35	27	34	23	33

*pT category in the pTNM classification of the Union Internacional Contra la Cancrum

Curability

Successful curative resection was defined as that in which cancer-free surgical margins were obtained and lymph node metastasis was restricted to the extent of the dissected area on postoperative histological examination.

Curative resection was achieved in 36 (55 per cent) of the 66 resected patients, in 30 of 44 patients who underwent hepatectomy, but in only six of the 22 patients who did not ($P < 0.01$).

Histological findings pT category

Microscopic tumour extension according to local extent of tumour (pT category in the pTNM pathological classification¹⁵) was examined. There was no lymph node metastasis, invasion of lymphatics or veins, or perineural infiltration in the four patients with pT₁ tumours. The 62 patients with pT₂ or pT₃ tumours, however, had a high incidence of lymph node metastasis, lymphatic permeation, venous invasion and perineural infiltration (Table 4).

Extramural tumour extension and front of the tumour. Microscopic extramural tumour extension was investigated in detail in 28 patients with pT₂₋₃ tumours who underwent curative resection. Extramural tumour extension was found in 23 patients; the mode of extension was perineural infiltration in 20, lymphatic permeation in 19, and venous invasion in four.

In five patients who were negative for microscopic extramural tumour extension, the front of the tumour in the longitudinal direction was part of the main tumour in every specimen. In the 23 patients with extramural tumour extension, on the other hand, extension often exceeded the front of the main tumour in the hepatic and/or duodenal direction. The front of the tumour was

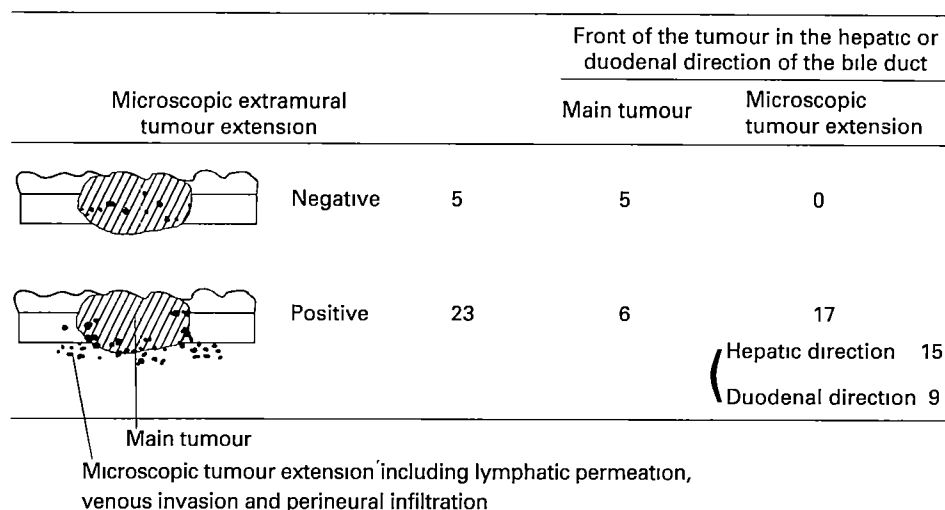


Fig. 1 Microscopic extramural tumour extension and front of the tumour in 28 cases of curative resection

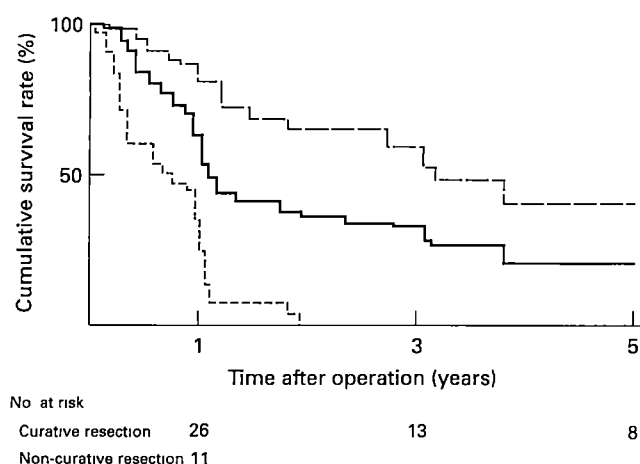


Fig. 2 Overall cumulative survival rate for the 66 resected patients (—) and cumulative survival rates for those who had curative ($n=36$; —) and non-curative ($n=30$; ----) resection. $P<0.01$ (curative versus non-curative; χ^2 test)

attributable to extramural tumour extension in 17 cases, more commonly in the hepatic direction (15 cases) than the duodenal direction (nine cases) but there was no significant difference between the two groups (Fig. 1).

Invasion to the caudate lobe. Microscopic tumour invasion to the caudate lobe was examined in 21 patients who had undergone caudate lobectomy: nine were found to have invasion to the caudate lobe. There were three different modes of invasion: (1) infiltration along the epithelium to the bile ducts draining the caudate lobe in five patients, (2) direct invasion or metastasis to the parenchyma of the caudate lobe in four, and (3) periductal spread to the interstitium of the caudate lobe in two patients.

Survival

The overall cumulative survival rates in the 66 resected patients are shown in Fig. 2. After curative resection, the cumulative 1-, 3- and 5-year survival rates were 85, 60 and

41 per cent respectively, whereas after non-curative resection all patients died within 2 years ($P<0.01$).

The 44 patients who underwent hepatectomy had a higher survival rate than the 22 patients who did not; however, the difference between the survival curves in these two groups was not significant.

Long-term survival

Of the 66 surgically treated patients, eight survived for more than 5 years after operation and six of these for more than 10 years. Three patients had so-called 'early cancer of the bile duct', which means that the tumour was pT_{1a} or pT_{1b} . The other five patients had pT_2 tumours with lymphatic permeation, venous invasion or perineural infiltration. None of these long-term survivors, however, had lymph node metastases. Additionally, all had a tumour-free surgical margin.

Discussion

Bile duct tumours should be regarded more as a regional than a local disease. Because bile ducts have thin walls, biliary tumours can easily involve surrounding tissues as they spread along the periductal lymphatic network and veins, and the perineural lymph clefts. They may also infiltrate the bile duct wall submucosally over a wide area¹⁶⁻¹⁸. Only four of the 66 patients who underwent resection for carcinoma of the hepatic duct confluence in this series had a pT_{1a} or pT_{1b} tumour with no lymph node metastases, no invasion of lymphatics or veins and no perineural infiltration. By contrast, these extensions were more frequent in patients with invasion of the subserosal or serosal layers, or adjacent organs, namely pT_2 or pT_3 tumours.

Surgical curability requires that no microscopic residual tumour be present, and thus knowledge of the histological spread of these tumours is essential to ensure clear surgical margins. The survival and recurrence-free rates for patients with tumour-free surgical margins were better than in those with involved surgical margins or residual macroscopic disease. This indicates the importance of extensive preoperative and perioperative assessment so that resection is performed only when it is potentially

curative and inappropriate extensive resection is avoided¹⁹. *En bloc* resection of carcinoma of the hepatic duct confluence has been attempted to achieve free surgical margins and long survival^{5,9,16,17}. Although many surgeons would support aggressive resection, the results of surgery on carcinoma of the hepatic duct confluence have been unfavourable because most of these tumours infiltrate major blood vessels (e.g. the hepatic artery or portal vein) and the liver parenchyma around the hepatic hilum, including the caudate lobe.

In Japan, successful curative resection for carcinoma of the bile duct has been defined as that in which cancer-free surgical margins are obtained and lymph node metastasis is restricted to the extent of the area dissected as demonstrated by postoperative histological examination²⁰. With respect to surgical margins, it has also been proposed that the cut edges of the bile duct in the hepatic and duodenal direction as well as the dissected plane in the transverse direction should have an intact segment extending at least 5 mm from the front of tumour extension^{16,17,20}. It is difficult to obtain such a long segment in the dissected plane in the transverse direction, especially when the tumour is located near the hepatic hilum, because the hepatic artery and portal vein travel close to the bile duct in the middle and upper third of the extrahepatic bile duct¹⁸.

Ouchi *et al.*²¹ reported achieving histologically curative resection (i.e. tumour-free resection margins) in only 16 of 36 patients treated surgically. Beazley *et al.*⁸ reported four patients with tumour-free margins in a total of 16 resections. In the present series, even when the patients underwent resection, it was sometimes difficult to perform curative procedures, and the attempt was successful in only 36 of 66 patients. Furthermore, an intact segment at least 5 mm from the tumour front was obtained in only five of the 66 resections (8 per cent).

It has been emphasized repeatedly that tumour cells often remain after radical resection that are apparently complete macroscopically, and that the risk of residual cancer markedly increases after local resection alone^{16,17,22}. This finding was confirmed by the results of the present study; invasion at the surgical margin was far more frequent in the patients who did not undergo hepatectomy than in those who did. Beazley *et al.*⁸ reported that a tumour-free surgical margin was obtained in seven of 16 patients who underwent resection, most of whom had undergone hepatectomy. Some authors^{23,24} have stated that in patients with very advanced disease, the tumour tends to spread extensively along the hepatic ducts, is more likely to invade the right hepatic artery than the left, and can be removed only by extensive resection of the bile ducts combined with hepatic lobectomy. Thus, local resection without hepatectomy is likely to leave cancer cells at the surgical margin and contribute little to improving survival. Nevertheless, when carcinoma of the hepatic duct confluence could be radically resected by local resection the outcome was significantly better than in patients with non-curative local resection. In the present series, hepatectomy was performed aggressively with caudate lobectomy in most patients with this disease, even in those with pT₃ tumours, and yet four patients with pT₁ or pT₂ tumours who underwent local resection only have survived more than 5 years after surgery. Thus, survival of patients does not appear to differ significantly according to whether they undergo hepatectomy.

Since 1982 the authors have emphasized the need for concomitant resection of the caudate lobe when right or

left hepatectomy is performed for radical surgery of carcinoma of the hepatic duct confluence¹⁶. Some authors^{7,22,23} who agree with this opinion have stated that adequate tumour clearance can be obtained by hepatectomy only with concomitant resection of the caudate lobe, and that local resection of the extrahepatic bile ducts together with the hilar bile duct is unlikely to be associated with long-term survival. The difficulty of performing concomitant resection of the caudate lobe, however, has discouraged many surgeons from undertaking the procedure. In this series, the caudate lobe was resected in 39 patients; histological study of tumour invasion of the hepatic hilum revealed cancer cells in the caudate lobe as well as in the bile duct draining this lobe in nine of 21 patients.

Boerma *et al.*²⁵ proposed *en bloc* resection of the hepatoduodenal ligament by right trisegmentectomy, with resection of the extrahepatic bile ducts, portal vein and hepatic artery to extirpate cancer cells in the hepatoduodenal ligament. Extension of the resection to vascular segments in the hepatoduodenal ligament was performed successfully after the first report of this technique by Longmire *et al.*²⁶ in 1973. Major hepatectomy, including resection and replacement of the complete hepatoduodenal ligament, has been shown to be feasible anatomically and experimentally, and the clinical results from Japan are promising^{27,28}. Boerma²⁹ concluded that current methods of resecting carcinoma of the hepatic duct confluence cannot totally eradicate this tumour, and that extending the resection in the retro hilar and hepatoduodenal directions might improve the long-term results. *En bloc* resection of carcinoma of the hepatic duct confluence has been performed by total hepatectomy followed by liver transplantation³⁰. The authors do not believe that the role of liver transplantation in the treatment of carcinoma of the hepatic duct confluence has yet been defined.

Important factors influencing long-term survival after curative resection include the histological diagnosis, tumour involvement of the surgical margins and lymph node metastasis. When all these factors are favourable, 5- and 10-year survival is indeed possible. Although uncommon, the papillary variant of carcinoma at this site is associated with a much better prognosis (a doubling of the survival rate) in the authors' experience³¹. Ouchi *et al.*²¹ reported a close correlation between the morphological features of carcinoma of the hepatic duct confluence and outcome. Papillary tumours were found in half of the 3-year survivors, and papillary or well differentiated adenocarcinoma in the remaining 3-year survivors. In the present eight long-term survivors, the histological grade of three tumours was papillary adenocarcinoma, and four tumours were well differentiated adenocarcinoma. None of these patients had lymph node metastasis.

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Laparoscopic treatment of symptomatic cysts of the liver

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Background Reports of successful treatment of liver cysts by the laparoscopic approach prompted the use of this technique in a series of patients.

Methods Ten patients with symptomatic liver cysts were treated by the laparoscopic deroofing technique. Eight patients had one solitary cyst, one had two cysts and the remaining patient had polycystic disease with a giant cyst. Hydatid disease was excluded serologically and radiologically but albendazole was used before operation in six cases because hydatid disease is endemic in Argentina.

Results There was no surgical morbidity or death. For between 6 months and 3 years all patients were asymptomatic. Computed tomography showed recurrence of a cyst in one patient, who was successfully reoperated on laparoscopically.

Conclusion Laparoscopic fenestration of either solitary or multiple liver cysts is the treatment of choice. It produces minimal surgical trauma, shorter hospital stay and avoids the morbidity of laparotomy. Reduced postoperative adhesions allows repeated procedures if the condition recurs.

Liver cysts are benign congenital malformations, probably resulting from isolated aberrant biliary ducts. They contain clear serous fluid. Generally, they do not invade biliary or vascular elements and if they attain large dimensions may cause atrophy of the liver parenchyma¹. Intracystic haemorrhage, rupture, torsion and infection may occur². The cysts may be single, multiple or diffuse (polycystic liver disease). Polycystic disease of the liver may be associated with involvement of the kidneys. Cysts are generally diagnosed by computed tomography (CT) or ultrasonography^{3,4}. Most patients are asymptomatic, and should not be treated.

Fenestration or deroofing is the treatment of choice³. The fluid of the cyst generally contains no bile or micro-organisms and has an electrolytic composition similar to that of plasma.

Laparoscopic surgery may provide similar results to open fenestration techniques, but hospitalization is shorter and the morbidity of laparotomy is avoided.

The purpose of this study was to evaluate surgical laparoscopic fenestration in ten patients.

Patients and methods

From January 1992 to July 1996 ten patients were referred for treatment of severe symptomatic liver cysts. There were nine women and one man. Mean age was 43 (range 25–65) years.

Dull pain in the upper abdomen was the most common symptom. One patient presented with acute intense pain in the right upper quadrant of the abdomen, probably due to intracystic haemorrhage. In five of these patients the liver was enlarged to the umbilicus.

Hydatid disease was screened for by serology (Antigen 5) and evidence of eosinophilia. The patient with polycystic disease had normal liver function test results and his kidneys were not involved.

CT and ultrasonography showed emergent cystic lesions, with no calcification or papillary projections in nine patients (Fig. 1). In one case ultrasonography found septa in the cyst. One patient had two cysts; in six cases the cyst was in the right lobe and in three on the left. In one patient, the studies failed to demon-



Fig. 1 Left hepatic lobe cyst

strate that the cyst of the right hepatic lobe also involved the left lobe. The cysts measured 5–18 cm in diameter. In two patients, the cyst had almost replaced the right lobe of the liver.

CT of the patient with a polycystic liver showed a large anterior cyst involving both right and left lobes and numerous small cysts.

As hydatid disease is endemic in Argentina, all patients were treated with albendazole for 30 days, although serological tests, ultrasonography and CT scans were negative.

Under general anaesthesia, four trocars were inserted. The first was inserted in the umbilicus by the open technique. Aspiration of the cysts was performed and 400–1200 ml were obtained; this was serous in nine patients and tainted with blood in the patient with acute abdominal pain. The cysts were deroofed with the Lin approach⁵, excising the walls up to the liver tissue. Haemostasis of the liver parenchyma was obtained by cautery or clips.

Omentum was introduced into the cyst cavity in six patients. All cysts were drained.

Results

The mean hospital stay was 4 (range 3–6) days. No postoperative complications were recorded. Pathological

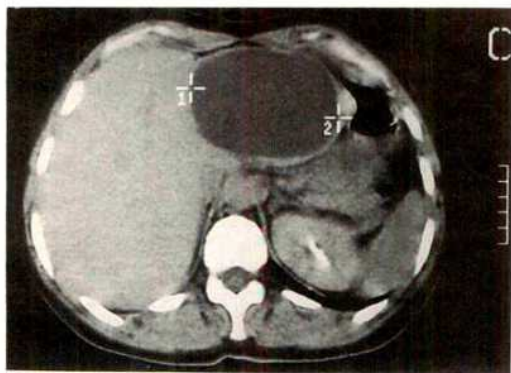


Fig. 2 Recurrent hepatic lobe cyst

studies of the wall of the cysts were typical of benign liver cysts.

Between 50 and 800 ml of serous fluid were recovered from the drains, which were removed after a median of 4 (range 3–8) days.

In the patient with the polycystic liver only the largest cyst was treated. Three months later CT identified a cyst on the left lobe in one patient (Fig. 2). The previous operation had treated a large cyst on the right lobe. A review of the CT scan showed that the primary cyst had involved the left lobe but had not been recognized. At reoperation no adhesions were present and the cyst of the left lobe was treated by fenestration.

All patients were asymptomatic for between 6 months and 3 years. On follow-up CT and ultrasonography, the liver was of normal size with no recurrence of the cysts. In the patient with a polycystic liver, there was no increase in size of the other cysts. One patient died 2 years later from diabetic coma.

Discussion

Most hepatic cysts are asymptomatic, and do not require treatment. Sixteen per cent of patients may complain of abdominal discomfort or pain⁵. Huge cysts may produce abdominal distension or dyspnoea. Acute pain is generally due to intracystic haemorrhage⁶.

Abdominal pain was present in all patients. The liver was enlarged and, in one case, intracystic haemorrhage was responsible for the acute pain.

Liver function is usually not altered, even in polycystic liver disease. In these cases the kidneys must be studied to ascertain involvement of the liver. Serological studies (Antigen 5) for hydatid disease were performed in all patients.

Although there was no proof of parasitic involvement of the cysts, as a precaution six patients were treated with albendazole before operation ($10 \text{ mg kg}^{-1} \text{ day}^{-1}$ for 1 month)⁷. Although laparoscopic treatment of hydatid liver disease is in the developmental stage, every effort should be made for an exact diagnosis⁸.

Percutaneous aspiration has a high recurrence rate (50 per cent) although good results can be obtained⁹, especially if alcohol sclerotherapy is used. Alcohol destroys the cells of the cyst but does not affect its walls, thus explaining the high failure rate¹⁰. Since Lin *et al.*³ described the technique, fenestration or deroofting of the cysts has become the treatment of choice. Fenestration creates free communications between the cyst and the

peritoneal cavity. Fluid from the cysts is either reabsorbed by peritoneum or extracted by drains located in the cyst cavity.

Open surgery provides good results^{1,2,11–14} with the deroofting technique. Complete resection of the cyst carries a high risk¹⁵. Blood vessels and bile ducts adjacent to the walls of the cyst can be injured easily, so resection must stop at the liver parenchyma so that deroofting is performed with minimal risk¹².

Laparoscopy has become popular^{2,5,10–13,15–23} for the treatment of liver cysts. The morbidity of laparotomy is avoided and most of the emergent cysts can be treated successfully. Laparoscopy provides access to almost all emergent solitary cysts. Best results are obtained in cysts of segments 4, 5, 6 and 7. In polycystic livers only the largest cysts should be treated^{11,2,11–14}.

In six patients omentum was placed in the cavity as it diminishes the size of the cavity and may prevent recurrence of the cyst^{6,9,15,21–24}. Drains help to reduce the amount of fluid reabsorbed from the peritoneal cavity. Renal insufficiency with ascites is a contraindication for fenestration¹⁹.

The deroofting technique was complication-free and the blood vessels of the adjoining hepatic tissue were coagulated or clipped. Postoperative CT showed no alterations in the liver of patients with large cysts. The patient with the recurrent cyst was asymptomatic, and the diagnosis was made on follow-up CT. At reoperation no adhesions were found and the cyst was successfully treated. Treatment of recurrent cyst after open surgery is complicated by adhesions from the previous operation. This problem is obviated in recurrences after laparoscopic fenestration¹² as occurred in one of the present patients.

In conclusion this report suggests that the laparoscopic approach allows successful deroofting of cysts and avoids large abdominal incisions with a short hospitalization period. If the cyst recurs, laparoscopy can be performed because of the lack of adhesions from previous treatment.

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Increased plasma levels of atrial natriuretic peptide and endocrine markers of volume depletion in patients with obstructive jaundice

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Background Hypovolaemia may cause renal dysfunction in obstructive jaundice. This study investigated whether, in patients with obstructive jaundice: (1) atrial natriuretic peptide (ANP) is increased; (2) fluid-regulating hormones are altered; and (3) biliary drainage improves fluid homoeostasis.

Methods Forty-three patients with obstructive jaundice were investigated. A renal profile was obtained and levels of ANP, renin, aldosterone and vasopressin were determined. In a subset of 18 patients, studies were repeated 3 days after endoscopic biliary drainage and changes in extracellular volume were measured.

Results Creatinine clearance was impaired in ten of 30 patients. Patients with obstructive jaundice had higher mean levels of ANP (118 *versus* 40 pg/ml, $P = 0.0001$) and aldosterone (156 *versus* 43 pg/ml, $P = 0.0001$) than matched controls. Increased renin levels were observed in ten of the 43 patients and were associated with impaired creatinine clearance. After biliary drainage ANP concentration decreased (110 *versus* 67 pg/ml, $P = 0.004$) as well as aldosterone level (182 *versus* 85 pg/ml, $P = 0.0002$) and the mean extracellular volume increased (20.5 *versus* 23.1 per cent of body-weight, $P = 0.001$).

Conclusion Plasma ANP concentration is increased in obstructive jaundice. Endocrine markers of hypovolaemia are activated in obstructive jaundice. After biliary drainage there is an improvement of endocrine and fluid derangements.

In 1960 Williams *et al.*¹ reported that dogs with prolonged obstructive jaundice had a reduction in plasma volume and required less blood loss to develop hypovolaemic shock than healthy animals. Indirect evidence of the relevance of appropriate volume replacement has been provided by studies showing the potential detrimental effects of forced diuresis in obstructive jaundice² and the beneficial effects of appropriate rehydration³. Direct evidence of marginal hypovolaemia in obstructive jaundice was recently provided from body water compartment analysis using trace isotopes, both in an experimental model and in humans^{4,5}. Hypovolaemia may explain why patients with obstructive jaundice are more prone to develop renal failure than non-jaundiced subjects in a wide range of facilitating circumstances such as sepsis, haemorrhage or administration of nephrotoxic drugs^{6,7}.

Plasma levels of atrial natriuretic peptide (ANP) were found to be paradoxically raised in rabbits with common bile duct ligation compared with sham-operated controls⁸, and further experiments revealed that endocrine alterations compatible with low extracellular volume, such as increased plasma renin activity, aldosterone and vasopressin plasma concentrations, were present in rabbits with common bile duct ligation⁹. In humans, however, no systematic studies have been carried out to investigate alterations of the water- and sodium-regulating hormones in obstructive jaundice. The present study investigated whether ANP is also increased in patients with obstructive jaundice and whether this increase can be reversed by endoscopic biliary drainage. Furthermore, the presence of

volume depletion and its possible correction after biliary drainage were investigated with endocrine markers and bioimpedance.

Patients and methods

In a longitudinal prospective observational study, 51 patients with obstructive jaundice were investigated. Patients with acute cholangitis, previous intravenous fluid therapy, use of diuretics, heart disease, parenchymal liver disease and chronic renal failure were excluded. Written informed consent was obtained. The following clinical data were recorded: age, sex, duration of jaundice and aetiology of obstructive jaundice. At admission, before therapy was started, values for the following were determined: bilirubin, alkaline phosphatase, haematocrit, electrolytes, creatinine, urea, albumin, ANP, plasma renin activity, aldosterone and vasopressin. Diuresis, creatinine clearance, natriuresis and sodium excretion fraction were determined in 24-h urine collections.

In a subset of 18 patients (ten women and eight men with a mean age of 66 years; six with benign and 12 with malignant disease), endoscopic internal biliary drainage with insertion of a 12-Fr polyethylene endoprosthesis was carried out. After biliary decompression, these patients were given 2500 ml glucose-saline infusion (150 mEq sodium chloride) on the first day and from the second day they were offered a defined oral diet of 2000 kcal, 80 g protein and 80 mEq sodium. Three days after biliary drainage, renal function tests and hormone determinations were repeated. Extracellular water volume variations occurring during the first 72 h after biliary decompression were assessed by calculating the fractional volume increase from changes in serum albumin levels and by bioimpedance. Fractional changes in extracellular volume were calculated using the formula: $(\text{Alb}_{\text{pre}}/\text{Alb}_{\text{post}} - 1) \times 100$, where Alb_{pre} and Alb_{post} represent albumin concentrations before and 3 days after biliary drainage¹⁰,

assuming that there were no significant albumin losses during the 3 days after drainage. Extracellular volume was also measured by bioimpedance with a BIA-101S apparatus (Laboratory RJI System, Mount Clemens, Michigan, USA).

Standard laboratory tests were carried out with a Synchron CX7 autoanalyser (Beckman-Astra Instruments, Brea, California, USA). Radioimmunoassay techniques were used to determine ANP (h-ANP, I-AR55; Eicken Chemical, Tokyo, Japan; reference values 20–60 pg/ml), plasma renin activity (Gamma Cob., TM (I-125); INCSTAR, Stillwater, Minnesota, USA; reference values 2–6–36 pg/ml), plasma aldosterone (Aldosterona Maia, Cob. 12 254; Biodata, Rome, Italy; reference values 10–80 pg/ml) and vasopressin (Buhlmann, RK-AR1, Allschwil, Switzerland; reference values 2–10 pg/ml). A group of 14 healthy subjects matched for age and sex were used as controls for hormone measurements.

Results are expressed as mean(s.d.). Intergroup and intra-group statistical analysis was carried out using the two-tailed Student's *t* test for unpaired and paired data. When data were not distributed normally, comparisons were made with the Mann-Whitney *U* or Wilcoxon signed rank tests. The Spearman correlation coefficient (r_s) was calculated to assess the correlation between variables. Data processing was done with a Macintosh LCII (Apple, Cupertino, California, USA) and the Statview II statistical package (Abacus Concepts, Berkeley, California, USA). Statistical significance was set at $P < 0.05$.

Results

Demographic and baseline data

Of the 51 patients assessed initially, 43 were included in the study. There were 21 men and 22 women aged 69(11) years. Accurate creatinine clearance determination was possible in 30 patients, of whom ten showed values below 70 ml/min. These patients had the same degree of diuresis (1360 versus 1511 ml per 24 h) but a higher sodium fractional excretion (0.8(0.6) versus 0.4(0.3) per cent, $P = 0.02$) than patients with creatinine clearance above 70 ml/min. All other renal parameters and hormone levels were similar in the two groups. Hypoalbuminaemia (less than 35 g/l) was observed in 30 patients and correlated inversely with bilirubin level ($r_s = -0.48$, $P = 0.007$) and positively with creatinine clearance ($r_s = 0.51$, $P = 0.01$). It was more often detected in patients with malignancy than in those with benign disease (22 of 28 versus five of 12; $P = 0.02$).

Endocrine changes

Patients with obstructive jaundice showed a threefold increase in plasma level of ANP compared with controls (Table 1). This increase was time independent since ANP

Table 1 Baseline endocrine profile of patients admitted with newly diagnosed obstructive jaundice compared with a control group

	Obstructive jaundice (n = 43)	Healthy controls (n = 14)	P
Age (years)	69(11)	64(13)	n.s.
Sex ratio (M:F)	21:22	8:6	n.s.
ANP (pg/ml)	118(46)	40(16)	0.0001
Plasma renin (pg/ml)	24.5(32.0)	9.6(5.4)	n.s.
Aldosterone (pg/ml)	156(72)	43(20)	0.0001
Vasopressin (pg/ml)	6.1(3.5)	n.a.	

Values are mean(s.d.). ANP, atrial natriuretic peptide; n.s., not significant; n.a., data not available (Mann-Whitney *U* test)

concentrations were identical (119 pg/ml) in short or prolonged obstructive jaundice (less or more than 15 days). Plasma aldosterone concentration was also increased. A high renin plasma concentration at admission (greater than 36 pg/ml) was observed in ten of 43 patients. Hyper-reninaemic patients had a lower creatinine clearance (53(20) versus 90(46) ml/min, $P = 0.03$) and a higher plasma aldosterone concentration (200(95) versus 141(56) pg/ml, $P = 0.02$). No correlations were found between serum bilirubin level or duration of jaundice and the plasma concentration of any water- and sodium-regulating hormone. There was a weak correlation between plasma renin and aldosterone levels ($r_s = 0.39$, $P = 0.001$).

Benign versus malignant jaundice

Table 2 shows a comparison of renal and endocrine parameters between benign and malignant jaundice. Cholestasis was more severe in patients with periampullary tumours, but differences in albumin, urea, creatinine, aldosterone and vasopressin levels between the two groups seem to indicate more severe volume depletion in patients with benign disease. Despite the fact that duration of jaundice was longer in the group of patients with malignancy, these differences cannot be attributed to duration of jaundice because there was no difference between patients with jaundice of short duration (less than 15 days) and those with a more protracted course, independent of the nature of disease. Only in benign biliary obstruction was there a positive correlation between ANP and plasma creatinine levels ($r_s = 0.65$, $P = 0.03$).

Changes after internal biliary drainage

After successful endoscopic-internal biliary drainage, the magnitude of the fall in bilirubin concentration was proportional to the pre-drainage bilirubin level ($r_s = 0.65$, $P = 0.006$). There was a decrease in ANP concentration and in that of endocrine markers of hypovolaemia, and a positive fluid balance as determined by changes in serum albumin concentration and bioimpedance (Table 3). There was no correlation between changes in ANP and bilirubin

Table 2 Comparison of baseline renal parameters and water- and sodium-regulating hormones in patients with benign or malignant obstructive jaundice

	Benign (n = 13)	Malignant (n = 30)	P
Duration of jaundice (days)	12(8)	19(13)	0.04
Total bilirubin (mg/dl)	11.7(6.0)	16.5(7.7)	0.05
Alkaline phosphatase (units/l)	289(201)	606(424)	0.01
Urea (mg/dl)	39(13)	28(12)	0.01
Creatinine (mg/dl)	1.1(0.4)	0.8(0.2)	0.01
Creatinine clearance (ml/min)	85(51)	78(42)	n.s.
Serum sodium (mEq/l)	138(2)	136(3)	0.05
Sodium excretion fraction (%)	0.5(0.3)	0.6(0.5)	n.s.
Serum albumin (g/l)	35(5)	30(5)	0.01
ANP (pg/ml)	111(57)	121(41)	n.s.
Plasma renin (pg/ml)	19(20)	26(36)	n.s.
Aldosterone (pg/ml)	199(69)	136(65)	0.004
Vasopressin (pg/ml)	8.3(4.2)	5(3)	0.02

Values are mean(s.d.). ANP, atrial natriuretic peptide; n.s., not significant. Student's *t* test for unpaired data; Mann-Whitney *U* test

Table 3 Metabolic changes in 18 patients with obstructive jaundice undergoing endoscopic internal biliary drainage

	Baseline	72 h after biliary drainage	P
Total bilirubin (mg/dl)	15(6)	8(4)	0.0001
Alkaline phosphatase (units/l)	562(446)	358(255)	0.008
Creatinine clearance (ml/min)	85(41)	72(30)	n.s.
Haematocrit (%)	40(5)	36(3)	0.0002
Serum albumin (g/l)	33.2(4.7)	29.8(3.6)	0.003
Extracellular volume BIA (% of body-weight)	20.5(3.4)	23.1(3.0)	0.001
Natriuresis (mEq per 24 h)	52(20)	63(37)	0.04
Sodium excretion fraction (%)	0.53(0.33)	0.82(0.74)	n.s.
ANP (pg/ml)	110(45)	67(46)	0.004
Plasma renin (pg/ml)	31.2(42.0)	12.6(10.4)	n.s.
Aldosterone (pg/ml)	182(85)	85(45)	0.0002
Vasopressin (pg/ml)	7.3(3.4)	7.6(4.6)	n.s.

Values are mean(s.d.). BIA, bioelectrics impedance analysis; ANP, atrial natriuretic peptide; n.s., not significant. Student's *t* test for paired data; Wilcoxon signed rank test

or alkaline phosphatase levels. The fall in serum albumin level after biliary drainage was used to calculate the fractional increase in the extracellular volume which amounted to 10(10) (95 per cent confidence interval 4–16) per cent. This was in agreement with the magnitude of the increase detected by bioimpedance. The volume of fluid gained did correlate with vasopressin level after drainage ($r_s = 0.8$, $P = 0.0006$) but not with plasma renin or aldosterone concentration either at baseline or after biliary drainage. There was also a good correlation between diuresis on day 3 and the magnitude of the increase in fractional sodium excretion ($r_s = 0.63$, $P = 0.008$). Vasopressin changes followed closely the decrease in alkaline phosphatase values and were associated with changes in the sodium excretion fraction (Fig. 1).

Discussion

This study reveals extensive endocrine derangements in human obstructive jaundice involving several hormones regulating sodium and water homeostasis. The concentration of ANP was increased threefold and remained raised as long as jaundice was not relieved. These findings agree with those obtained from laboratory animals. Oms *et al.*⁸ first reported increased ANP levels in rabbits submitted to bile duct ligation. Subsequent studies confirmed that ANP concentration rose immediately after bile duct ligation⁹. Arterial and venous blood sampling and immunohistochemical studies indicated that the heart was the most probable source of ANP^{9,11}. In these experiments, the animals also exhibited marked hypodipsia and hypophagia and showed inappropriate diuresis and natriuresis. Similarly, in the present study population, patients exhibited a relatively high fractional sodium excretion and normal diuresis although aldosterone levels were increased and a significant proportion of patients had impaired creatinine clearance (less than 70 ml/min). This implies that in obstructive jaundice ANP is effective

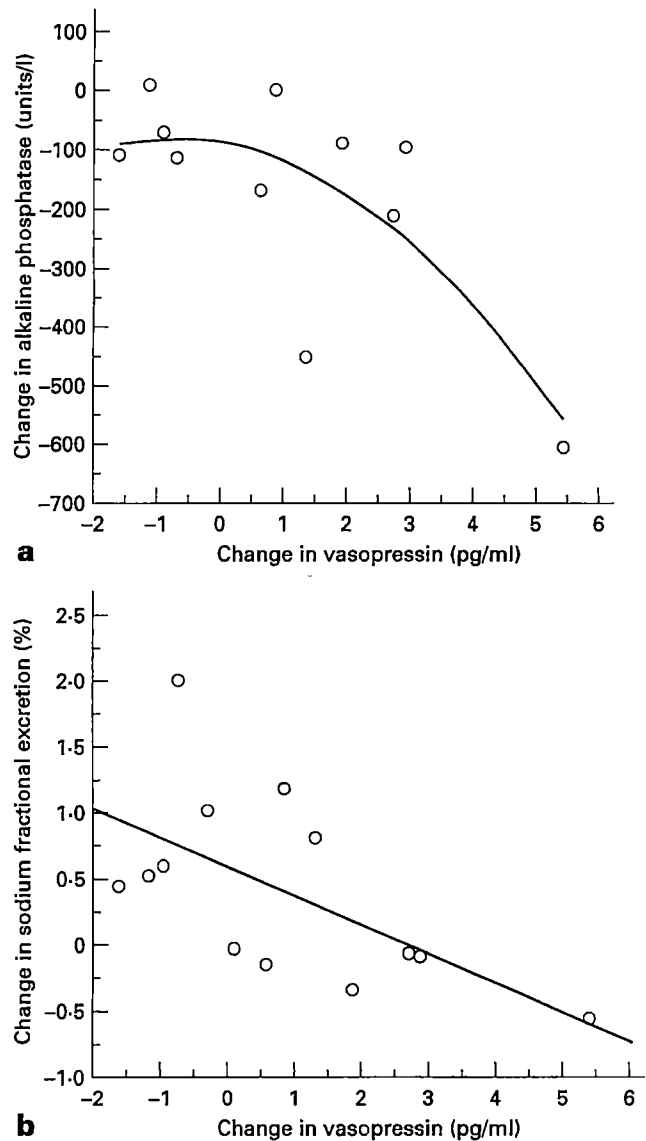


Fig. 1 Correlation between change in plasma vasopressin concentration and a change in alkaline phosphatase level ($r_s = 0.74$, $P = 0.04$) and b change in sodium fractional excretion on the third day after biliary drainage ($r_s = 0.60$, $P = 0.03$)

in inducing natriuresis despite a reduced glomerular filtration rate.

ANP concentration increases paradoxically in obstructive jaundice without concomitant expansion of the circulating blood volume. Furthermore, ANP concentration starts to decrease just after biliary drainage despite a parallel expansion of the extracellular volume. Thus, in obstructive jaundice, increased levels of ANP are not secondary to hypervolaemia, the only well known factor inducing ANP release¹², but a 'primary' phenomenon that may be linked with minimally disturbed cardiac function.

Hyperbilirubinaemia may induce ANP release by decreasing cardiac performance. Green *et al.*¹³ showed a reduced rate of increase of left ventricular pressure in animals with a choledochocaval fistula. Recent work suggests that basal cardiac contractility is affected in rats 3 days after common bile duct ligation¹⁴. Because ANP is

a sensitive marker of myocardial dysfunction¹⁵, increased levels may be secondary to subclinical heart dysfunction. Using a variation of the model of Green *et al.*¹³, the present authors found a more pronounced increase in ANP concentration after construction of a biliovenous shunt than after bile duct ligation¹⁶. Taking these data together, it seems reasonable to hypothesize that in obstructive jaundice there is a subclinical myocardial dysfunction that leads to atrial distension and increased secretion of ANP. Myocardial dysfunction and marginal hypovolaemia could act synergistically in producing the renal and haemodynamic disturbances observed in obstructive jaundice. This, however, remains speculative since no haemodynamic studies have been reported in humans with obstructive jaundice.

Plasma renin and aldosterone levels are also increased in patients with obstructive jaundice. Marginal increases of plasma renin activity and significant hyperaldosteronism in experimental obstructive jaundice were initially reported by Hishida *et al.*¹⁷ and subsequently confirmed by Valverde *et al.*⁹. In these investigations, plasma aldosterone level was inappropriately high for the renin concentration. The present study confirms these findings. Aldosterone concentration was increased in most of the present patients whereas renin was increased in only ten of 43. Thus, it seems that in obstructive jaundice aldosterone secretion may be activated through a renin-independent pathway. In addition, these findings suggest that chronically raised plasma ANP concentrations, up to threefold over normal values, cannot suppress aldosterone secretion as was hypothesized initially¹⁸ and, in consequence, the renal effects of the peptide can be partially masked by a coexisting hyperaldosteronism.

After biliary drainage there was a tendency towards normalization of the altered hormonal pattern, an increase in the sodium excretion fraction and a positive fluid balance. Renin and aldosterone values were reduced by half. The decrease in alkaline phosphatase level correlated with an increase in vasopressin concentration and this probably contributed to the expansion of the extracellular water compartment. These data suggest that biliary drainage may be helpful in improving hydration in patients with biliary obstruction.

In summary, it has been shown that ANP concentration is increased in humans with extrahepatic biliary obstruction, as part of an extensive endocrine derangement involving the other hormones regulating fluid and sodium balance. After internal biliary decompression, there is a hormonal shift towards normalizing fluid homeostasis. Altered hormonal patterns and, possibly, heart dysfunction may underlie the haemodynamic and renal disturbances observed in obstructive jaundice.

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Laparoscopic management of acute peritonitis

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Background The presence of peritonitis has previously been considered to be a contraindication for the laparoscopic approach because of the theoretical risk of malignant hypercapnia and toxic shock syndrome. The aim of this retrospective study was to demonstrate that laparoscopy is feasible, safe and efficient in cases of peritonitis.

Methods From January 1990 to July 1995, 231 patients had a laparoscopy for acute peritonitis in two centres (91 appendicular peritonitis, 69 gastroduodenal perforated ulcers, 35 perforations of the colon, 36 miscellaneous).

Results The diagnostic accuracy of laparoscopic exploration was 84.8 per cent. The clinical preoperative diagnosis was changed by laparoscopic exploration in 25.1 per cent of patients. An unnecessary laparotomy was avoided in 6.5 per cent of patients and the site of traditional incision was modified in 8.7 per cent. Conversion rates were 25 per cent for appendicular peritonitis, 16 per cent for gastroduodenal perforation and 83 per cent (29 of 35 patients) for colonic perforation. The overall mortality rate was 3.9 per cent. No malignant hypercapnia occurred. Two patients (0.9 per cent) had postoperative septic shock but survived.

Conclusion Laparoscopy is feasible and safe in cases of peritonitis. Laparoscopic treatment is particularly effective in the case of appendicular and gastroduodenal perforation. In the case of colonic perforation, the conversion rate remains high but with growing experience and surgical skill, more of these cases will be treated laparoscopically in the future.

Until recently, the presence of peritonitis was considered to be a contraindication to laparoscopy^{1,2}. Two major arguments supported this contraindication. First, the theoretical risk of malignant hypercapnia due to an increased absorption of carbon dioxide in the presence of severe intra-abdominal infection and inflammation of the peritoneum. Second, the risk of toxic shock syndrome by increased passage of bacteria and toxins into the circulation, because of the increased intraperitoneal pressure^{3,4}. The aim of this study was to determine whether laparoscopic management of peritonitis is feasible, safe and efficient. Advantages of the laparoscopic approach were defined.

Patients and methods

From January 1990 to July 1995, about 900 laparoscopies were performed for acute abdominal pain in two academic departments of surgery. Acute peritonitis was found in 231 patients whose notes were reviewed retrospectively. The need for laparoscopy was determined by a trained laparoscopic surgeon experienced in emergency abdominal surgery. The diagnosis of peritonitis was based on the laparoscopy and the finding of purulent fluid in the peritoneal cavity. Peritonitis was scored according to the Mannheim Peritonitis Index (MPI) (Table 1) and the Acute Physiology And Chronic Health Evaluation (APACHE) II score^{5,6}. The presence of shock or major ileus was considered to be a contraindication to laparoscopy.

All patients underwent operation in the supine position under general anaesthesia, bladder catheterization was carried out. Pneumoperitoneum was created with a Veress needle inserted in the left hypochondrium or in the umbilicus at a maximum pressure of 12 mmHg. Exploration of the peritoneal cavity was performed after introduction of the optical system through a

10-mm umbilical port. Further ports were placed according to the nature of the disease. In the presence of diffuse peritonitis, the first step was to evacuate purulent collections and to perform abundant irrigation of the four abdominal quadrants with isotonic saline at 37°C delivered by a high-flow irrigation-suction device. Once the diagnosis had been established, patients were either managed laparoscopically or underwent conversion to an open procedure. Drains were inserted routinely at the end of the operation. Diagnostic accuracy and therapeutic results of laparoscopy were evaluated according to the origin of the peritonitis.

Results

The study included 231 patients (121 women and 110 men) with a mean age of 49 (range 12–93) years. Generalized peritonitis was present in 54.1 per cent of patients. The overall postoperative mortality rate was 3.9

Table 1 Mannheim Peritonitis Index

Risk factor	Weighting if present
Age > 50 years	5
Female sex	5
Organ failure*	7
Malignancy	4
Preoperative duration of peritonitis > 24 h	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, purulent	6
Faecal	12

*Kidney, lung, shock, intestinal obstruction

per cent (nine of 231 patients). Mean MPI and APACHE II scores were 20.1 and 5.7 respectively. Consequently, the expected theoretical mortality rates (TMR) were 4 and 12 per cent⁵⁻⁷.

The exact cause of peritonitis was established by laparoscopy in 84.8 per cent of patients (196 of 231). In 34 patients, conversion to laparotomy was necessary to clarify the diagnosis suspected at laparoscopy. Most of these cases (25 of 34) presented as perforation of the colon that could not be localized by laparoscopy. In one case (0.4 per cent) a wrong diagnosis was made at laparoscopy: an appendicular abscess was mistaken for pancreatic necrosis. This patient had a second laparoscopic exploration on the eighth postoperative day establishing the correct diagnosis, and an appendicectomy was performed laparoscopically. The clinical preoperative diagnosis was changed by laparoscopic exploration in 58 cases (25.1 per cent) and an unnecessary laparotomy was avoided in 15 of these patients (6.5 per cent) (ten with pelvic inflammatory disease, two with acute ileitis, one with diverticulitis without perforation, one with carcinomatosis of colonic origin and one with acute pancreatitis). In 20 patients (8.7 per cent) who underwent conversion to open operation, laparoscopy precipitated a change in the site of the incision or limitation in its size. Causes of peritonitis and diagnostic accuracy are listed in Table 2.

Appendicular peritonitis was present in 91 patients with a mean age of 42 (range 12–83) years. Mean MPI and APACHE II scores were 18.6 and 3.9 respectively (TMR 3 and 9 per cent respectively). Mean operative time was 75 (range 30–150) min. The conversion rate was 25 per cent (23 cases). In most of these cases conversion was related to difficulties with dissection. Mean hospital stay was 8 days. One 83-year-old patient died after conversion to laparotomy, giving a mortality rate of 1 per cent. He had peritonitis from a perforated appendix and suffered wound dehiscence on day 13 after operation. Death was due to pulmonary embolism on day 17. The morbidity rate was 9 per cent (eight of 91 patients). Only one complication was related directly to the laparoscopic approach. A small bowel loop incarcerated in the umbilicus was injured while introducing the first port; the bowel was sutured at open operation. No further complications occurred. A rapidly corrected septic shock occurred in an 18-year-old patient in the recovery room after laparoscopic management of an appendicular abscess. Two other complications occurred in patients whose procedure was converted: one wound abscess and

one case of respiratory failure. In the group of patients treated successfully by laparoscopy, there were also two cases of pneumonia, one pelvic abscess and one small bowel obstruction.

Sixty-nine patients presented with perforated gastroduodenal ulcer. Their mean age was 52 (range 20–93) years. In 93 per cent of patients, suture of the perforation was performed. The mean operative time was 100 (range 55–180) min. The conversion rate was 16 per cent (11 of 69 patients); six of these conversions resulted from inability to locate the site of the perforation. The mean hospital stay for gastroduodenal perforation was 13 days. Mean MPI and APACHE II scores were 20.7 and 6.7 respectively (TMR 6 and 14 per cent respectively). The mortality rate in this series was 4 per cent (three patients). Two high-risk patients (aged 93 and 87 years) died from cardiac failure. The third patient was an 87-year-old woman whose operation was converted to laparotomy for disseminated gastric cancer. She died after abdominal dehiscence 21 days after operation. The morbidity rate was 13 per cent (nine patients).

Perforation of the colon was found in 35 patients. The mean age in this group was 67 (range 32–88) years. Mean Mannheim and APACHE II scores were 22.3 and 8.9 respectively (TMR 8 and 18 per cent respectively). In 17 of these patients a wrong preoperative diagnosis of gastroduodenal or appendicular perforation was corrected by laparoscopy. The procedure was converted to open operation in 29 of 35 patients with perforation of the colon. In 25 patients the site of the perforation could not be identified, and in four patients the laparoscopic diagnosis was corrected after laparotomy. In six patients laparoscopic management was attempted: two colostomies were assisted laparoscopically for perforation of the sigmoid colon and two patients had laparoscopic drainage of a pericolic abscess. In two patients, presenting with perforation after colonoscopy, a laparoscopic suture of the perforation was performed successfully. Three of 35 patients with perforation of the colon died, nine suffered complications and the mean hospital stay was 18 days.

Miscellaneous causes of peritonitis are presented in Table 2. Two patients died in this heterogeneous group. A 70-year-old patient in poor general condition with disseminated gallbladder carcinoma died from secondary biliary peritonitis. A second patient died from multiple organ failure after conversion to laparotomy for intestinal infarction. Five patients had laparoscopic exploration for postoperative peritonitis. Four of these patients had a pelvic or subdiaphragmatic abscess. In one patient biliary

Table 2 Causes of peritonitis, diagnostic and therapeutic results

Aetiology of peritonitis	Total	Correct laparoscopic diagnosis	Conversions	Complications	Mean hospital stay (days)
Appendicitis	91	91	23 (25)	8 (9)	8
Perforated ulcer	69	63	11 (16)	9 (13)	13
Perforation of the colon	35	10	29 (83)	9 (26)	18
Pelvic inflammatory disease	14	14	0	0	6
Small bowel perforation	7	6	4	4	15
Biliary peritonitis	6	5	2	2	10
Postoperative peritonitis	5	5	0	0	7
Primary peritonitis	1	0	0	0	12
Acute pancreatitis	1	1	0	0	12
Urinary peritonitis	1	1	0	0	6

Values in parentheses are percentages

peritonitis was due to cystic duct necrosis after laparoscopic cholecystectomy.

Discussion

The aim of this study was to assess the usefulness of laparoscopy as a diagnostic and therapeutic tool in the management of peritonitis. The feasibility, safety and advantages of laparoscopy over conventional open surgery were considered. All the patients were included on the basis of a single diagnostic criterion: the presence of purulent fluid in the peritoneal cavity⁸.

The feasibility of laparoscopy in the presence of an acute abdominal condition has been demonstrated even if for some entities the conversion rate remains high. In the literature, the diagnostic accuracy of laparoscopic exploration in emergencies is reported to be about 90 per cent^{9,10}. In acute peritonitis, a slightly lower percentage of correct diagnoses (84.8 per cent) was obtained in the present study because a laparoscopic diagnosis was considered to be correct only if the exact origin of the peritonitis was identified. Thorough exploration of the abdominal cavity is difficult in emergencies, especially in the presence of peritonitis. Difficulties with exposures are related to inflammation and dilatation of bowel loops, sometimes making manipulation by laparoscopic forceps dangerous. When there is ileus and a dilated bowel, the routine use of open laparoscopy is recommended. Peritoneal hyperaemia absorbs a lot of light thus diminishing the quality of the image. Half of the conversions in this study were due to incomplete diagnosis. Most of these patients presented with colonic perforation, but would have required conversion for therapeutic reasons anyway.

The feasibility of laparoscopic treatment was demonstrated in perforated gastroduodenal ulcer and appendicular peritonitis. Only three patients (4 per cent) with gastroduodenal perforation required conversion to an open procedure for therapeutic reasons, because of the need for gastrectomy in two cases and pyloroplasty in one. Difficulties with dissection represent the major reason for conversion in appendicular peritonitis. Adhesions, usually separated by finger dissection, have to be managed with laparoscopic forceps without sensorial feedback. Laparoscopic treatment is rarely possible in cases of colonic perforation. In the presence of a tumour, all procedures were converted. Laparoscopic management of malignancy is controversial^{11,12} and it seems wise to withhold laparoscopic treatment in the presence of malignancy associated with peritoneal inflammation. In perforated diverticular disease and in selected cases, a two-stage operation could be undertaken: laparoscopic lavage and drainage of the peritoneal cavity, followed 3 months later by a laparoscopic colectomy. O'Sullivan and colleagues¹³ have recently recommended treating suppurative peritonitis due to perforated diverticular disease of the pelvic colon by laparoscopic peritoneal lavage, antibiotics and intravenous fluid replacement.

Laparoscopy for postoperative peritonitis is a new concept and should be used with caution. Open laparoscopy is mandatory instead of the blind introduction of a Veress needle; few cases will be suitable for laparoscopic treatment. Best indications are postoperative infected collections unsuitable for percutaneous drainage.

Until recently, peritonitis was considered as a contraindication to carbon dioxide pneumoperitoneum because of the risks of severe hypercapnia and dissemination of

infection. With experience of successful laparoscopic management of acute cholecystitis and appendicitis the authors started to treat more severe intra-abdominal infections laparoscopically. No death was specifically related to the laparoscopic approach. In this series a single complication (perforation of the ileum) was related to laparoscopy (0.4 per cent).

The use of carbon dioxide for creation of pneumoperitoneum can induce hypercapnia and respiratory acidosis. In the presence of inflammation with hyperaemia and alteration of capillary permeability, increased absorption of carbon dioxide is possible. At the same time alteration of pulmonary function by sepsis can impair adequate carbon dioxide elimination. No case of hypercapnia was seen in this study but assisted hyperventilation was employed as soon as end-tidal carbon dioxide exceeded 38 mmHg to eliminate excess carbon dioxide from the blood.

In these patients, pneumoperitoneum did not seem to have disseminated the infection. However, two patients (0.9 per cent) presented with septic shock after operation. One of these patients was admitted more than 24 h after perforation of a peptic ulcer with diffuse purulent peritonitis. Conversion to open operation was carried out and the patient presented with shock only several hours after the procedure. In the second case, the shock was corrected rapidly in the recovery room, and blood cultures remained sterile. Two experimental studies have provided contradictory results on the danger of pneumoperitoneum in the presence of peritonitis^{14,15}. Unfortunately, these studies did not include a laparotomy control group. Gurtner *et al.*¹⁶ studied the effect of a 1-h pneumoperitoneum compared with that of a 10-cm laparotomy in rabbits with experimental peritonitis; there were no differences between the two groups in terms of dissemination of infection. Collet *et al.*¹⁷ showed that clearance of bacteria from the peritoneal cavity in pigs is faster following laparoscopy than after laparotomy, laparoscopy inducing less impairment of local and general defence mechanisms. Furthermore, carbon dioxide was demonstrated to act as a bacteriostatic agent that could impair bacterial replication¹⁸.

In this series the mortality rate was low (3.9 per cent) because many patients presented with gastroduodenal or appendicular perforation¹⁹⁻²⁵. Additionally, patients with severe preoperative shock were excluded from laparoscopy. Death occurred exclusively in older patients with a mean age of 80 (range 63-93) years and an American Society of Anesthesiologists grade of III or more. Three of these patients presented with disseminated cancer. This mortality rate of 3.9 per cent has to be compared with the mortality rate quoted for open series. The mean Mannheim score was 20.1 in this series predicting a theoretical mortality rate of 4 per cent. The mean APACHE II score was 5.7, predicting a mortality rate of 12 per cent. In patients presenting with an APACHE II score of between 6 and 15, the mortality rate was 7.6 per cent, which is comparable to that for most open series^{7,18,26}. Using the Mannheim score, Billing *et al.*²³ have defined mortality rates in a multicentre series of 2003 patients undergoing laparotomy for peritonitis. The results of the present study suggest that laparoscopy does not increase the mortality rate in the management of peritonitis (Table 3).

This study shows diagnostic and therapeutic advantages of laparoscopy. An erroneous preoperative diagnosis was corrected by laparoscopic exploration in one-quarter of

Table 3 Mortality rates according to Mannheim scores

Mannheim score	Mortality rates (%)	
	Laparotomy*	Laparoscopy (present study)
<21	2.3	0.8
21–29	22.5	6.8
>29	59.1	13

*Data from Billing *et al.*²³

patients thus avoiding an 'unnecessary' laparotomy in 6.5 per cent. In 20 patients who required an open procedure, laparoscopy changed the site of the incision for conversion. The negative laparotomy rate for suspected peritonitis has been estimated to be 4 per cent. This rate has remained unchanged over four decades (1950–1989)²⁷. It is estimated that laparoscopy could avoid 10 per cent of unnecessary laparotomies performed for the clinical suspicion of peritonitis.

Although the conversion rate was high (29.9 per cent), especially in the case of colonic perforation (29 of 35 patients), laparoscopic treatment was achieved in 70.1 per cent of patients in this series. The advantages of laparoscopic treatment of peritonitis are not only the cosmetic aspects but the virtual absence of parietal complications. Postoperative abdominal wound dehiscence is virtually eliminated after laparoscopy. In 69 patients who underwent conversion there were two cases of abdominal dehiscence (3 per cent). Postoperative wound dehiscence is reported to be 2–10 per cent following midline laparotomy^{25–28}. No wound infection occurred in this series following laparoscopic treatment, compared with a reported wound abscess rate of 2–35 per cent^{19,22,25,28–30}. Several prospective studies have already demonstrated that the rate of wound infection is reduced after laparoscopic appendectomy^{30–33}. Pelvic abscess developed in 1.5 per cent of the present laparoscopically treated patients, a figure similar to that associated with laparotomy^{22,25,28–30,34}.

This study demonstrates that laparoscopic exploration is safe in the presence of diffuse peritonitis. Laparoscopic exploration is effective for diagnostic confirmation and planning of further treatment. Unnecessary laparotomy is avoided in 5–10 per cent of patients. Complete laparoscopic management is particularly effective in the case of appendicular and gastroduodenal perforation. In the case of colonic perforation, the conversion rate remains high but with growing experience and surgical skill, more of these patients will be treated laparoscopically in the future.

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Evaluation of ultrasonography and clinical diagnostic scoring in suspected appendicitis

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Background Several diagnostic aids have been developed to improve diagnosis in suspected appendicitis including ultrasonography and clinical diagnostic scoring. The aim of this study was to elaborate a new scoring system and to measure its accuracy in the preoperative diagnosis of appendicitis, comparing it with the available scoring systems.

Methods The clinical, radiological and ultrasonographic data of 192 patients with suspected appendicitis were collected prospectively.

Results Only six of the 12 variables analysed were shown to have prognostic significance. Using Bayesian methodology, a weight was given to each criterion and two overall scores were calculated (ultrasonographic and classical scores). A cut-off point was identified to separate patients who needed surgery and those for observation. The ultrasonographic score showed an 81 per cent sensitivity and a 96 per cent specificity, compared with 60 and 73 per cent respectively for the classical score.

Conclusion Ultrasonography increases the diagnostic accuracy in patients with suspected acute appendicitis.

Acute appendicitis is the most common disease leading to emergency abdominal surgery¹. Preoperative diagnosis of acute appendicitis remains challenging despite improvements in history taking and clinical examination, new computer-aided decision support systems, clinical diagnostic scoring and new imaging techniques such as ultrasonography² and computed tomography³.

Diagnostic scores are useful and easy methods which help a surgical decision to be reached. Their objective is to reduce the number of negative appendicectomies⁴. These scores make use of clinical, analytical and radiological findings to produce a rationalized model of clinical decision making.

Presently, at least 11 scores have been proposed to aid the diagnosis of acute abdominal pain^{5–15}, six focusing on appendicitis^{5–10}. Although all authors have reported excellent predictive accuracy in their series, few have confirmed the reliability in subsequent prospective studies^{6,9,10,11,13}.

Graded compression ultrasonography is useful in the diagnosis of appendicitis, and in some hospitals has become routine in patients with pain in the right lower abdominal quadrant.

The aim of this study was to compare the diagnostic accuracy of ultrasonography and the classical clinical factors employed in the diagnosis of acute appendicitis. Two scores were employed: one considered factors with well demonstrated diagnostic relevance according to the literature (classical score) and the other included ultrasonography in addition (ultrasonographic score).

Patients and methods

One hundred and ninety-two patients with pain in the right lower abdominal quadrant, lasting fewer than 7 days and who presented between November 1993 and July 1996, were reviewed. Ninety patients were men and 102 women. On admission, 11 items considered useful for the diagnosis of appendicitis were recorded. A radiologist, with no previous knowledge of the clinical symptoms, performed ultrasonography in all the patients. Patients in whom ultrasonography could not be performed and those with a clear diagnosis of acute appendicitis were excluded from the study (563 patients had appendicectomy for acute appendicitis in this interval).

After the initial evaluation, the patients either had surgery or were included in a follow-up group; none was discharged. The diagnosis of appendicitis was confirmed histologically in resected specimens.

Clinical details recorded for the study included initial location of pain, duration of symptoms, fever (temperature higher than 38°C), nausea or vomiting, diarrhoea (liquid faeces more than three times a day), right lower quadrant guarding (presence of voluntary or involuntary contracture of the abdominal muscles), signs of peritoneal irritability (rebound tenderness, Rovsing's and psoas signs), increased peristalsis, leucocytosis (more than 10 500 leucocytes per mm³) and left shift (presence of more than 75 per cent neutrophils or immature forms, band and/or metamyelocytes).

Signs suggestive of appendicitis on plain abdominal radiography were the presence of faecoliths, disappearance of the psoas line, focal ileus or increased density in the right lower quadrant.

The ultrasonographic examination was done using a high-definition Hitachi scanner EUB-515A (Sonotron) with a linear 7.5-MHz and a sectorial 3.5-MHz probe. The diagnosis of acute appendicitis was based on the appearance of pain on graded compression of the area, in which an abnormal appendix could be seen. Appendicitis was suggested by the presence of a tubular immobile non-compressible image that on transverse section appeared as a target with a diameter equal to or greater than

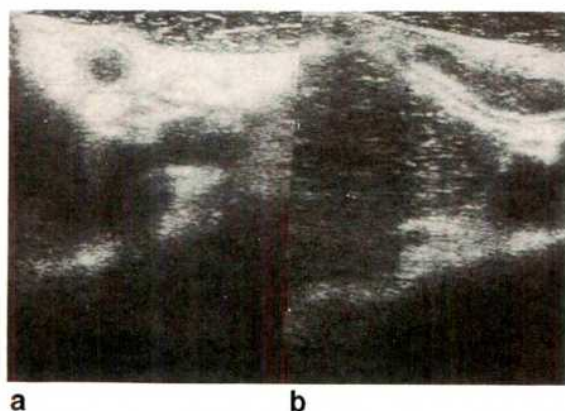


Fig. 1 a Transverse and b longitudinal ultrasonographic images in a patient with acute appendicitis showing the typical three-ringed (target) pattern

6 mm or with a wall thicker than 2 mm or a hyperechoic submucosa¹⁶ (Fig. 1). The presence of faecoliths or prominence of the periappendicular fat was an indirect sign. Ultrasonography was considered negative when the appendix could not be found or was normal, or if non-appendicular pathology was discovered.

Scoring system

The degree of association between each diagnostic factor and the presence of acute appendicitis was determined with the χ^2 test. Statistically significant factors ($P < 0.05$) were employed in the score and values of sensitivity, specificity, efficiency, positive and negative likelihood ratio, and relative risk were calculated for each factor.

In analysis of the results, the logistic regression model was discarded because of its complexity¹⁵. It was assigned a positive and negative diagnostic weight according to the following formulae¹⁷:

$$\begin{aligned}\text{Positive weight} &= 10 \times \ln[\text{sensitivity}/(1 - \text{specificity})] \\ \text{Negative weight} &= 10 \times \ln[(1 - \text{sensitivity})/\text{specificity}]\end{aligned}$$

Results of the weights were rounded to the nearest integer and, by addition of appropriate weights, a score was computed for

each variable. When analysing all the results, a cut-off point was established for both scores to obtain the maximum diagnostic accuracy.

Results

A total of 101 of 192 patients (53 per cent) had histologically confirmed appendicitis (50 acute focal, 16 suppurative, 27 gangrenous and eight perforated). Ninety-one patients (47 per cent) either had a non-inflamed appendix (17 patients underwent appendicectomy: five normal, four with minimal catarrhal changes¹⁸, five follicular lymphoid hyperplasia, two ovarian follicular cysts and one endometriotic cyst) or were discharged (74 cases) when their symptoms had settled after a median observation interval of 3.3 days. The absence of recurrent symptoms was confirmed 1 month later by further examination or telephone.

The age of the patients ranged from 3 to 88 (median 21.8) years; 52 per cent were younger than 14 years. The median age of patients with and without appendicitis was 24.1 and 19.3 years respectively (P not significant).

The initial location of the pain was in most cases epigastric (49 per cent), followed by the right lower quadrant (32 per cent), diffuse (10 per cent), right hypochondrium, right renal angle and hypogastrium. The typically described migration of pain from the epigastrium to the right lower quadrant was not significantly associated with appendicitis in this study.

Analysing the possible association between the prognostic variables recorded and the presence of appendicitis, only six were found to be significant (Table 1). Ultrasonography displayed the greatest diagnostic weight, with an 82 per cent sensitivity and 96 per cent specificity (18 false negatives and four false positives).

The values of the classical and ultrasonographic scores for each patient were calculated. The classical scores ranged from -21 to 20 for patients with appendicitis and from -31 to 13 for those with a normal appendix. The ultrasonographic score ranged from -26 to 50 for

Table 1 Significant predictive factors

	Appendicitis (n = 101)	Not appendicitis (n = 91)	χ^2	P	Diagnostic weight	Sensitivity (%)	Specificity (%)	Predictive value (%)		Accuracy (%)	Likelihood ratio		RR
								Positive	Negative		Positive	Negative	
Rebound tenderness													
Yes	61 (60)	40 (44)	4.29	0.03	3	60	56	60	56	58	1.36	0.71	1.9
No	40 (40)	51 (56)			-3								
Guarding													
Yes	82 (81)	57 (63)	7.12	<0.01	3	81	37	58	64	60	1.28	0.51	2.5
No	19 (19)	34 (37)			-7								
Leucocytosis													
Yes	83 (82)	49 (54)	16.60	<0.001	4	82	46	63	70	65	1.51	0.39	3.8
No	18 (18)	42 (46)			-9								
Neutrophil left shift													
Yes	82 (81)	44 (48)	21.40	<0.001	5	81	52	65	71	67	1.68	0.36	4.6
No	19 (19)	47 (52)			-10								
Abnormal abdominal radiograph													
Yes	21 (20)	1 (1)	15.13	<0.001	3	20	99	95	52	57	20.0	0.8	22.7
No	80 (80)	90 (99)			-2								
Ultrasonographic appendicitis													
Yes	83 (82)	4 (4)	111.40	<0.001	30	82	96	95	82	88	20.20	0.19	106.3
No	18 (18)	87 (96)			-16								

Values in parentheses are percentages. RR, relative risk

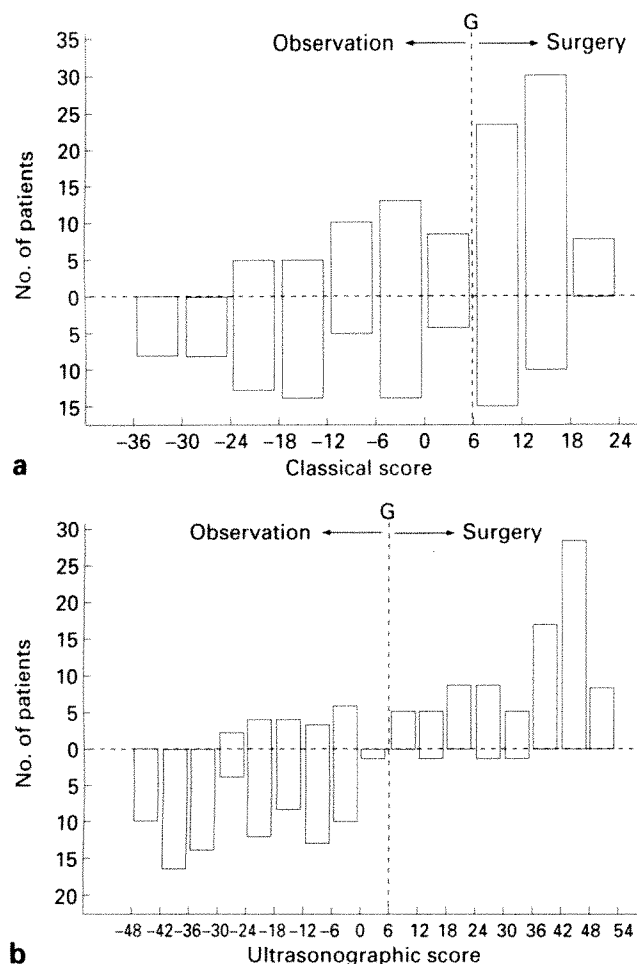


Fig. 2 Distribution of the frequencies according to the values of **a** classical and **b** ultrasonographic scores in 101 patients with and in 91 without acute appendicitis. For both the classical and ultrasonographic scores, point G was selected as the cut-off because of its maximum sensitivity and specificity

appendicitis and from -47 to 35 for the rest. Both scores were divided at six-point intervals (Fig. 2).

The theoretical sensitivity and specificity for each potential cut-off point were analysed. The receiver-operator characteristic curves for both scores are shown in Fig. 3. At point G, the maximum sensitivity and specificity were estimated as 60 and 73 per cent for the classical score and as 82 and 96 per cent for the ultrasonographic score.

Discussion

In 1986 Puylaert¹⁹ described the graded compression ultrasonographic technique for the diagnosis of acute appendicitis; several studies, including the present, have proved its high efficiency¹⁹⁻²⁸. Orr *et al.*²⁹ have done a meta-analysis including 17 previous studies (3358 patients) and showed an 84.7 per cent sensitivity and a 92.1 per cent specificity.

The sensitivity of ultrasonography is less than the specificity, because of the number of false negatives, some of which cannot be controlled (poor tolerance by the patient, obesity, presence of gas and unusual location of the appendix). These difficulties can be reduced by

	Point											
	A	B	C	D	E	F	G	H	I	J	K	L
Level of decision	-30	-24	-18	-12	-6	0	6	12	18	24	30	36
Classical score												
Sensitivity (%)		100	95	90	80	67	60	37	7			
Specificity (%)		17	32	47	52	67	73	89	100			
Ultrasonographic score												
Sensitivity (%)	100	98	94	90	87	81	82	76	71	63	55	50
Specificity (%)	43	48	61	70	84	95	96	96	97	97	97	100

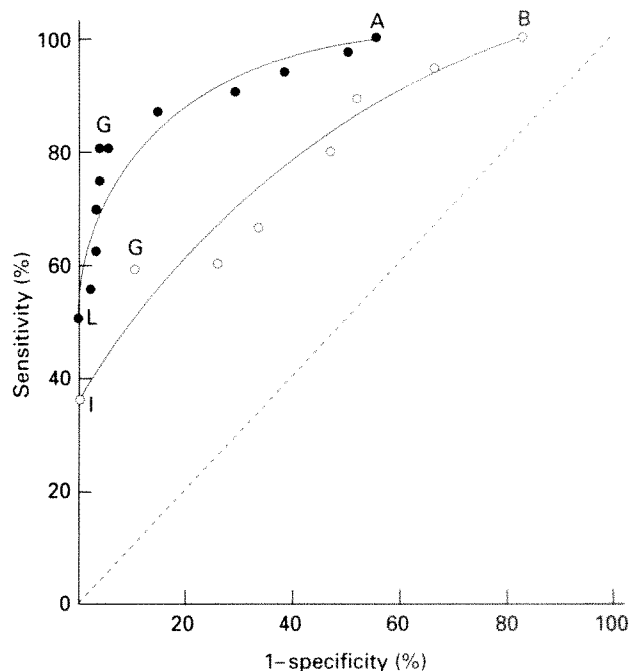


Fig. 3 Potential levels of decision for the scoring systems; the data are represented with a receiver-operator characteristic curve. ○, Classical score; ●, ultrasonographic score. Points A and B represent maximum sensitivity; I and L show maximum specificity; and points G for both scoring systems denote the selected cut-off point

employing high-resolution real-time imaging and by improving the graded compression technique²¹. In the present series, all 18 false negatives were due to failure to visualize the appendix, one-third owing to technical difficulties (five gas and one poor tolerance). Four of the false negatives were explained by inexperience of the radiologist.

The high specificity of ultrasonography is useful for the differential diagnosis of associated pathology such as mucocoele of the appendix, mesenteric lymphadenitis, acute ileitis, Crohn's disease or gynaecological disorders²⁰. There were four false positives (all by trainee radiologists). In two cases the radiologist was confident about the ultrasonographic diagnosis of appendicitis, but as the symptoms subsided the patients did not have surgery, so there was no tissue for histology to examine the radiological diagnosis. Some authors have reported an excessive number of false positives as a result of overvaluation of the target ultrasonographic image in children³⁰. In children the mucosa and submucosa are physiologically thicker³¹. Another alternative explanation is that the appendicitis resolved³². The third patient with

false-positive findings had a phlegmon in the right lower quadrant due to a ruptured follicular ovarian cyst. The fourth was a 13-year-old boy with a tubular non-compressible 6–7-mm image. The thickening of the submucosa was due to lymphoid follicular hyperplasia without appendicitis³².

Diagnostic scores and computer-aided decision-support systems apply the probability theory to use clinical, radiological and analytical data in the diagnosis of disease. The classical scoring system in this series had a higher sensitivity and a lower specificity than those reported by others (Lindberg and Fenyö¹⁴ demonstrated 57 per cent sensitivity, 80 per cent specificity and a cut-off point of –11; Fenyö⁶ found 53 per cent, 84 per cent and –7; Teicher *et al.*¹² found 49 per cent, 83 per cent and 1; Alvarado⁵ had 48 per cent, 85 per cent and 6; and Ramírez and Deus¹⁰ reported 77 per cent, 87 per cent and 10 respectively). The addition of ultrasonography to the classical score improved efficiency by 33 per cent. Sensitivity and specificity were the same for the ultrasonographic score and ultrasonography alone (81 and 96 per cent respectively) owing to the high diagnostic weight of ultrasonography. The addition of ultrasonography to scores employing more powerful factors⁴ might improve its efficiency alone.

Despite negative results reported by some³⁰, ultrasonography performed by trained radiologists is a valuable aid in the differential diagnosis of appendicitis. It is particularly useful in doubtful cases of appendicitis and, when used with a classical scoring system, improves the results obtained with the best diagnostic scores reported to date. The reliability and non-invasive nature of ultrasonography argue that it should be taken into account in the computer-aided decision-support systems to be designed in the future.

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Iron metabolism and erythropoiesis after surgery

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Background This was a prospective study comparing the effect of major and minor surgery on haematological variables concerning erythropoiesis, iron metabolism and acute-phase response proteins.

Methods Thirty-one otherwise healthy patients, 15 having major orthopaedic surgery and 16 undergoing minor surgery, were studied. Blood samples were taken before surgery and 1, 4, 10 and 28 days after operation.

Results Haemoglobin concentration was decreased for up to 4 weeks after surgery. Serum erythropoietin concentration and reticulocyte count were raised after major surgery only. Serum iron concentration dropped the day after major (to 23 per cent of its preoperative level) and minor (to 46 per cent of its preoperative level) surgery and remained lower for up to 28 days after major surgery. Serum transferrin concentration and transferrin saturation decreased after both types of surgery while ferritin concentration increased. Serum transferrin receptor concentration increased only 4 weeks after major surgery ($P < 0.01$). The interleukin 6 peak (day 1) was greater after major than minor surgery, as was the C-reactive protein peak (day 4).

Conclusion Both major and minor surgery induce a state of hypoferraemia in the presence of adequate iron stores. The degree of this transient form of 'anaemia of chronic disease' is related to the extent of surgery. Iron supplementation in the first weeks after surgery (if iron stores were normal before operation) is ineffective.

Anaemia after surgery could be explained by blood loss during and after operation. However, there is evidence that the characteristics of postoperative anaemia are more similar to those of the anaemia of chronic disease (ACD) rather than iron deficiency^{1,2}. ACD is seen in patients with inflammatory disorders and malignancy^{3–5}. This type of anaemia is characterized by a decrease in plasma iron and transferrin levels despite adequate iron stores, and a reduction in erythropoiesis^{3–5}. The mechanism of postoperative anaemia remains unknown although it could be an acute-phase 'inflammatory' effect of surgery^{6–10}. The contribution of tissue damage, anaesthesia and blood loss to the extent of anaemia was studied in patients undergoing major and minor surgery.

Patients and methods

Thirty-one patients were included; 15 had major elective orthopaedic surgery and 16 had a minor surgical procedure (minimal blood loss, short operation). Major surgery included total hip replacement (12 patients), total knee replacement (one) and laminectomy (two). Minor surgery was correction of hallux valgus/exostosis (seven), arthroscopy of the knee (two), shoulder arthroplasty (four), laparoscopic repair of inguinal hernia (two) and laparoscopic cholecystectomy (one). No patient had a history of chronic inflammatory disease and all had normal preoperative levels of haemoglobin, serum ferritin, folic acid and vitamin B₁₂. Participants in an autologous blood transfusion programme were excluded. No patient had evidence of postoperative infection or haemolysis. No oral iron supplements were allowed during the study. This study was approved by the Medical Ethical

Committee of Eemland Hospital. Informed consent was given by all patients.

Venous blood was taken at 08.00 hours on the day before the scheduled operation and on days 1, 4, 10 and 28 after operation. Total blood count was measured (E-5000 Hematology Analyser; Sysmex Toa, Kobe, Japan) including reticulocyte count (flow cytometric analysis; Sysmex R-1000)¹¹. Serum erythropoietin was measured by an enzyme-linked immunosorbent assay (ELISA) (Boehringer, Mannheim, Germany; normal range 0.4–9.0 units/l). Serum transferrin receptor was determined as described previously (normal range 3.8–7.2 mg/l)^{12,13}. Iron metabolism was further analysed by measuring serum iron (Hitachi 717; normal value 10–30 µmol/l), serum transferrin (normal value 2.2–3.6 g/l), transferrin saturation (calculated from serum iron and transferrin concentration; normal value 0.20–0.45) and serum ferritin (normal value 20–200 µg/l). C-reactive protein (CRP) was measured by turbidimetry (Hitachi 717, Boehringer, Mannheim, Germany; normal value 0–10 mg/l). Interleukin (IL) 6 (normal value less than 8 ng/l) and tumour necrosis factor (TNF) α (normal value less than 40 ng/l) were measured in serum using an ELISA^{14,15}.

Data are given as mean(s.d.). Statistical significance was assessed using Student's *t* test (two-sided). Non-parametric variables were tested with a χ^2 test. Correlations were analysed with the Mann-Whitney *U* test and Spearman rank correlation coefficient. Significance was accorded with a *P* value of less than 0.05.

Results

Demographic and perioperative characteristics are listed in Table 1. Blood transfusion was necessary in two patients with excessive blood loss (more than 1200 ml) after total hip replacement.

Mean preoperative values of all haematological variables tested did not differ significantly between the

Table 1 Demographic and perioperative characteristics of the 31 patients undergoing surgery

	Major surgery	Minor surgery
Sex ratio (F:M)	11:4	6:10
Regional anaesthesia	13	7
General anaesthesia	2	9
Age (years)	65(11)	61(10)
Blood loss during operation (ml)	553(279)	4(13)*
Blood loss after surgery (ml)	530(288)	7(20)*
Duration of operation (min)	127(33)	56(23)*
Intravenous fluids (ml)		
During operation	3400(400)	1300(800)*
After operation	1000(700)	300(800)†

Values are mean(s.d.). * $P < 0.001$, † $P < 0.05$ versus major surgery (Student's *t* test)

groups. Changes in haemoglobin and serum erythropoietin concentration are shown in Fig. 1. There was a small, non-significant increase in reticulocyte count 1 week after major surgery (preoperative value $68(19) \times 10^9/l$; maximum value $95(23) \times 10^9/l$). The changes in iron metabolism are shown in Fig. 2. The decrease in serum iron and transferrin concentration as well as in transferrin saturation the day after surgery was greater after major than minor surgery ($P < 0.01$). The acute-phase reaction after surgery is documented by an increase in serum ferritin and CRP (Fig. 3) and IL-6 concentration^{8,9}. The CRP peak after surgery was significantly higher after major surgery ($P < 0.01$). IL-6 concentration increased the day after surgery from 40(18) to 138(151) pg/ml after major surgery ($P < 0.01$) and from 30(14) to 62(45) pg/ml after minor surgery ($P < 0.01$) with a rapid fall thereafter. No significant increase in TNF- α concentration could be detected after surgery (data not shown). The relation between clinical data, markers of the acute-phase reaction and the haematological variables was tested. The duration of operation correlated significantly with the peak CRP level ($r_s = 0.65$, $P < 0.001$) and the blood loss correlated with the decrease in haemoglobin concentration the day after surgery ($r_s = 0.72$, $P < 0.001$). The lowest haemoglobin value after surgery correlated significantly with the peak serum erythropoietin concentration ($r_s = 0.49$, $P < 0.05$). Peak CRP concentration was proportional to the maximum decrease in serum iron ($r_s = 0.37$, $P = 0.05$) and transferrin ($r_s = 0.54$, $P < 0.01$) concentration as well as with the decrease in haemoglobin concentration on the day after surgery ($r_s = 0.69$, $P < 0.001$) and the peak serum erythropoietin concentration ($r_s = 0.66$, $P < 0.001$). No significant correlation could be found between the peak IL-6 concentration and the other haematological variables. In a subanalysis of the minor surgery group according to the method of anaesthesia (nine general, seven regional) no differences could be found with respect to changes in iron metabolism and erythropoiesis (results not shown).

Discussion

Postoperative anaemia has not been studied extensively because it was thought simply to be due to blood loss at operation. Such anaemia was easily treated with red blood cell transfusion and/or supplementation with iron. The

disadvantages of blood transfusion such as transmission of viral infections and impairment of the immune system have drawn attention to alternative options¹⁶. It has been shown that iron supplementation after hip surgery has no major effect on erythropoiesis^{1,2}. Analysis of the mechanism of postoperative anaemia may give more insight into changes in iron metabolism and may have clinical relevance.

In this study, surgery led to distinctive changes in iron metabolism: a decrease in the serum levels of iron and

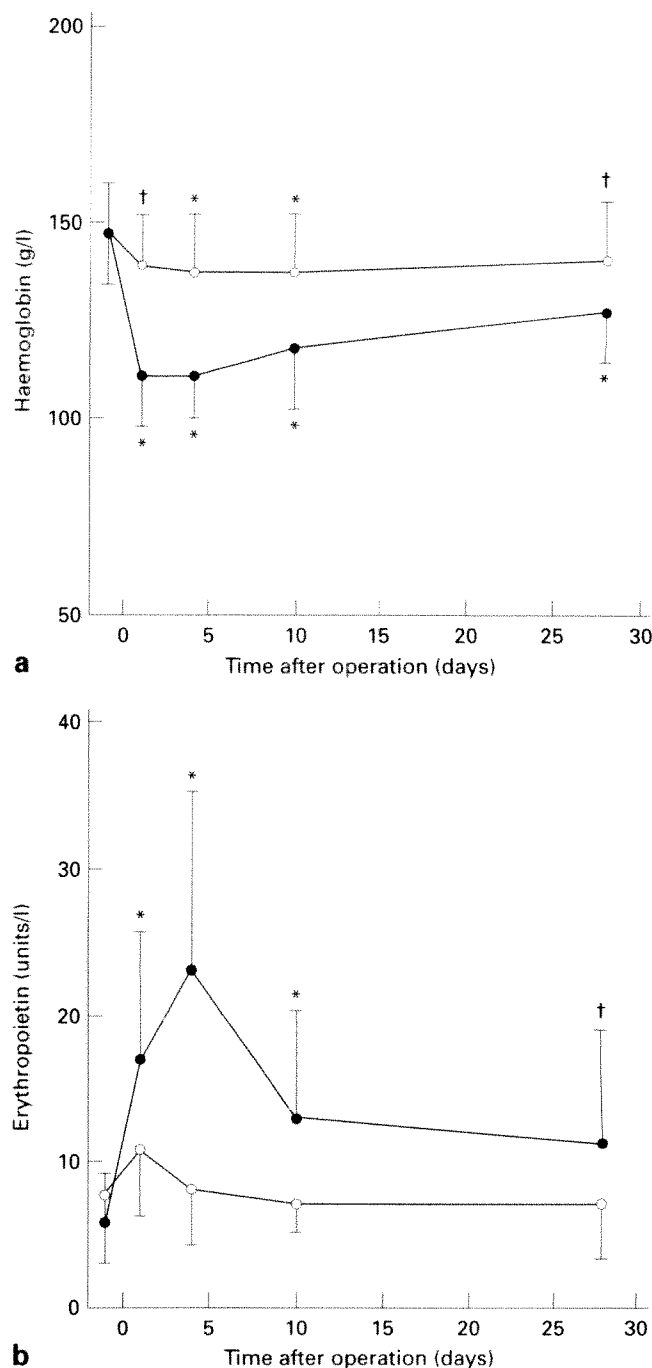


Fig. 1 a Mean(s.d.) haemoglobin concentration and b serum erythropoietin concentration in 31 patients undergoing major (●) or minor (○) surgery. * $P < 0.001$, † $P < 0.01$ versus preoperative value (Student's *t* test)

transferrin and in transferrin saturation, and an increase in serum ferritin concentration^{1,17-19}. These changes mimic those found in ACD and indicate a functional iron deficiency. This is in contrast to uncomplicated iron deficiency where low serum iron levels and transferrin saturation are accompanied by an increase in serum transferrin and a decrease in ferritin concentration. In the present patients serum transferrin receptor concentrations were normal (less than 6.0 mg/l) after surgery. An increase in these receptor values is seen in increased erythropoiesis as well as in iron deficiency (greater than

8.5 mg/l)^{12,20}. In ACD, serum transferrin receptor concentrations are believed to be normal²⁰. The hypothesis from this study is that after surgery signs of iron deficiency are overruled by those of anaemia of inflammation. In the first weeks after surgery, there is a failure of the bone marrow to increase erythropoiesis in response to the anaemia, as indicated by the minimal change in transferrin receptor levels or reticulocyte count. Only 4 weeks after major surgery was an increase in soluble transferrin receptor concentration observed, indicating increased erythropoiesis, while iron became

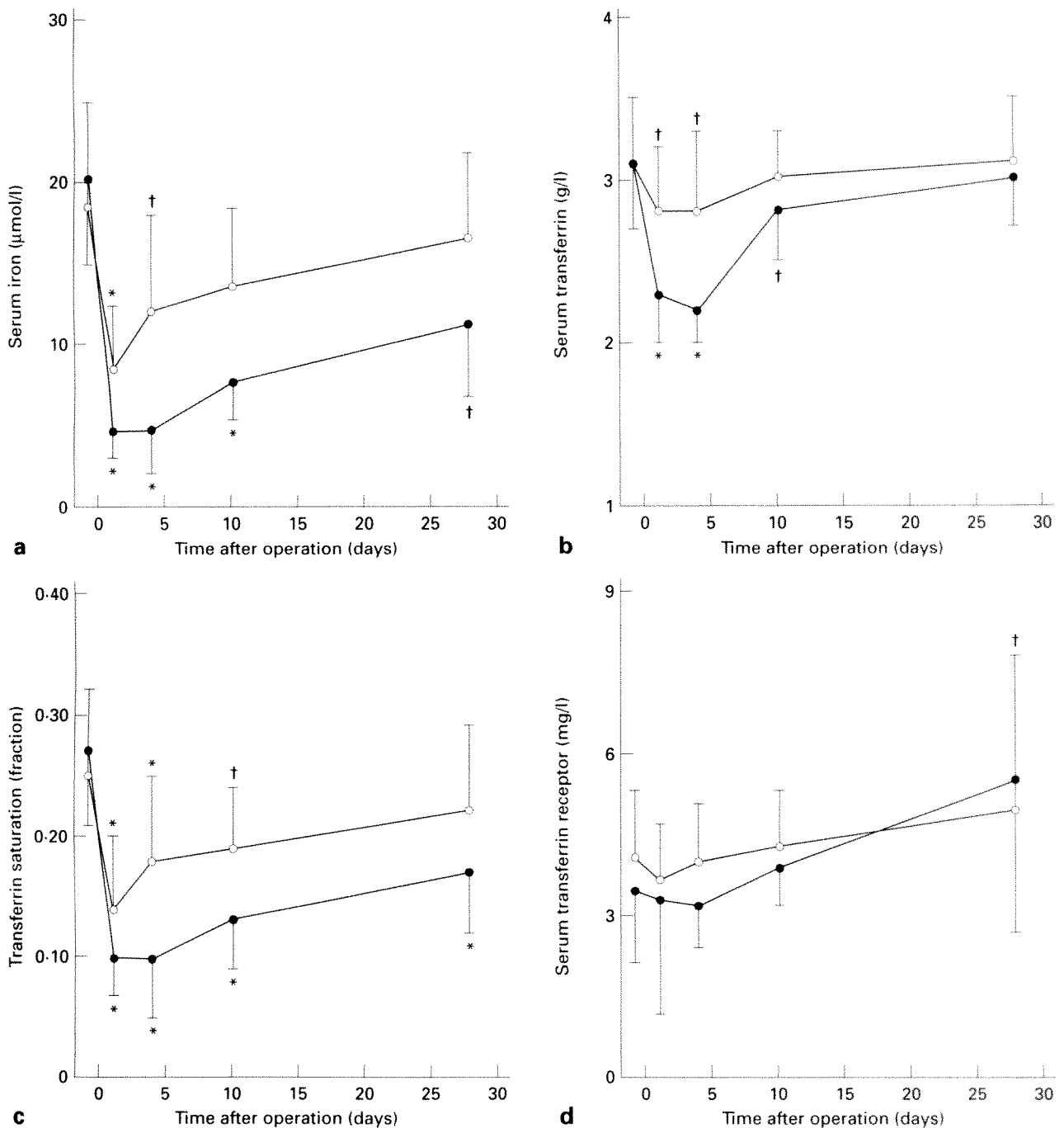


Fig. 2 Changes in iron metabolism in 31 patients undergoing major (●) or minor (○) surgery. Values are mean(s.d.); a serum iron concentration, b serum transferrin concentration, c transferrin saturation and d serum transferrin receptor concentration. * $P < 0.001$, † $P < 0.01$ versus preoperative value (Student's t test)

more available, reflected by increased serum iron levels and transferrin saturation. These findings explain the ineffectiveness of iron supplementation during the first weeks after surgery if normal iron stores are present before operation.

This study also shows that even minor surgery has a significant impact on iron metabolism, although changes are milder and recovery is faster than after major surgery. This indicates that blood loss is not essential in inducing changes in iron status. The method of anaesthesia seems

to have no influence, in accordance with a study on serum iron after hysterectomy using two different types of anaesthesia²¹. The extent of surgery does influence iron metabolism. A more major operation results in a greater and more prolonged change in iron parameters, suggesting that the changes in iron metabolism are related to tissue damage. A marked acute-phase response was found after both types of surgery, although it was greater after major surgery. The concentration of IL-6, one of the most important acute-phase mediators, was increased the day after surgery. The CRP level was greatest 4 days after operation. The production of CRP by hepatocytes is induced by IL-6²². No increase in TNF- α , another mediator of the acute-phase response, was found after surgery in this study. A direct relation between cytokines and altered iron metabolism is described in chronic inflammation^{5,23,24}. The release of cytokines leads to iron uptake by activated macrophages²⁵. Cytokines (IL-1, IL-6) are directly involved in increased ferritin synthesis, which is under translational control^{25,26}. In this study, the rise in CRP and fall in serum iron and transferrin concentration correlated significantly. Minor tissue damage can initiate an acute-phase reaction including the release of cytokines, and is sufficient to produce changes in iron metabolism.

Even 1 month after both types of surgery, the haemoglobin concentration had not returned to the preoperative level. This cannot be ascribed to perioperative blood loss, dilution or blood sampling for this study. The changes in iron metabolism and the relative unavailability of iron for erythropoiesis after surgery may contribute to this prolonged postoperative anaemia. The inflammatory cytokines may also have a direct influence on postoperative erythropoiesis⁵. IL-6 may, unlike IL-1, stimulate rather than depress erythropoiesis²⁷, but IL-6 also induces anaemia by increasing plasma volume^{28,29}. Further studies are necessary to gain more insight into a possible stress factor. An effect of cortisol has been suggested but is unlikely since cortisol concentration can be decreased after surgery too, similar to serum iron²¹.

In conclusion, both major and minor surgery induce a state of hypoferraemia in the presence of adequate iron stores, and a marked acute-phase response. The degree of this transient anaemia is related to the extent of the surgical insult. Iron supplementation in the presence of normal iron stores is ineffective at this time.

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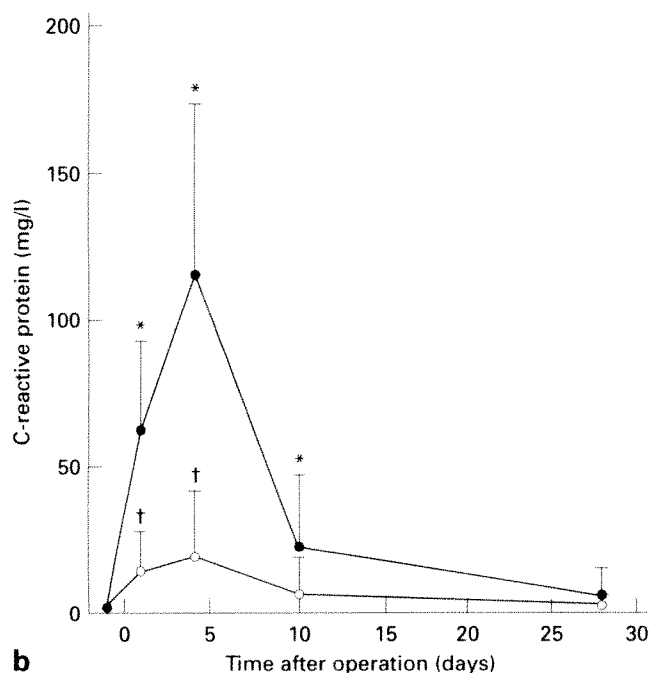
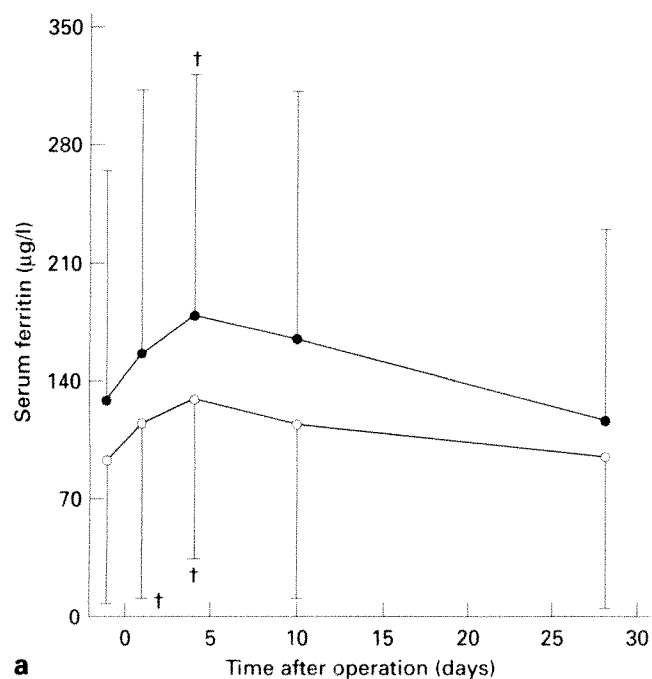


Fig. 3 a Mean(s.d.) serum ferritin and b C-reactive protein concentration in 31 patients undergoing major (●) or minor (○) surgery. * $P < 0.001$, † $P < 0.01$ versus preoperative value (Student's t test)

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Expression of c-myc oncoprotein represents a new prognostic marker in cutaneous melanoma

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Background Overexpression of the c-myc oncoprotein has been observed to be of prognostic significance in several human cancers. This study was undertaken to establish whether c-myc has any prognostic significance in melanoma.

Methods Expression of c-myc oncoprotein was studied in a prospective series of primary and secondary malignant melanomas. Ethanol-fixed tissue was digested into nuclei and stained for flow cytometric analysis using a pan-myc antibody.

Results Overexpression of the c-myc oncoprotein was prevalent in both disease stages. In primary disease, overexpression was associated with tumour thickness and with the presence of ulceration, age and reduced disease-free interval. Of most importance, high expression of c-myc predicted poor outcome in both primary and metastatic disease. In addition, c-myc was able to discriminate prognosis in melanomas uniformly stratified as thick (greater than 3 mm) lesions.

Conclusion These results indicate an important role for c-myc in melanoma which may lead to better prognostic information and identification of new therapeutic strategies.

The worldwide incidence of cutaneous melanoma has approximately doubled each decade for the past 50 years, particularly in Caucasians under 40 years of age¹. Surgical excision of thin primary tumours offers the best possibility of cure as melanoma is largely refractory to other modalities once it has metastasized. Thickness of the primary tumour remains the most important prognostic determinant². However, in a significant proportion of tumours, behaviour may not agree with that predicted by this parameter, even in 'thin' melanomas³. Furthermore, it is difficult to predict prognosis on an individual patient basis. The solutions to these clinical and epidemiological issues are only likely to follow greater understanding of melanoma biology and increasing attention has been directed at elucidating gene-led mechanisms in the genesis and behaviour of this disease⁴.

Tumours form as a result of a multistep process, involving perturbation of oncogenes⁵ that encode proteins to regulate cell growth and proliferation, often in response to epigenetic factors producing DNA injury. The c-myc gene lies on the long arm of chromosome 8q(24) and encodes a nuclear phosphoprotein of 62 kDa that is known to play a central role in the control of proliferation and differentiation of many normal and malignant tissues⁶. This gene appears to be intimately involved in regulating passage of cells through the cell cycle⁷ and directing cells towards apoptosis⁸. However, c-myc is unable to transform cells alone, and requires the co-operative action of other oncogenes, such as *ras*⁹.

Levels of expression of both c-myc messenger RNA (mRNA) and its encoded protein have been shown to be of prognostic importance in several cancers¹⁰, particularly those of the cervix¹¹, and head and neck¹², but only limited studies of the protein in clinical melanoma specimens have been published to date¹³. The aim of this study was to investigate c-myc oncoprotein expression in both primary and metastatic melanoma and observe whether

any relationship exists between protein levels and clinical behaviour.

Patients and methods

Specimens

Expression of c-myc oncoprotein was studied in 50 ethanol-fixed melanomas obtained from patients undergoing surgical excision of either a primary lesion or regional or distant metastases at this hospital. Tumour specimens were selected on the availability of material for flow cytometry which precluded many thin primary lesions. The series comprised 14 primary melanomas and 36 metastases. A portion of the fresh, dry sample was assigned to histological analysis and the remainder placed in 70 per cent ethanol and stored at 4°C until processed.

Preparation and staining of nuclei

A 3-mm³ sample of each specimen was minced and enzymatically enucleated in 10 ml 0.4 mg/ml pepsin solution in 0.1 mol/l hydrochloric acid (Sigma Chemical Company, Poole, UK). The mixture was agitated constantly at 37°C for 50 min and filtered through a 35-µm nylon mesh in a Swinnex holder. Nuclear concentration was adjusted to fewer than 10⁶ nuclei per mm³ and aliquoted into two samples before being washed twice in phosphate-buffered saline (PBS), centrifuging at 2000 r.p.m. for 5 min between cycles. One sample was used to assay c-myc oncoprotein while the second served as an isotypic control using an immunoglobulin (Ig) G antibody at the same protein concentration. A pan-myc-specific antibody was used to identify c-myc (Cambridge Research Biochemicals, Cambridge, UK). Antibody was added at a dilution of 1:25 in a 100-µl solution of PBS containing 0.5 per cent normal goat serum and 0.5 per cent Tween 20 (polyoxyethylenesorbitan monolaurate; Sigma Chemical Company) for 1 h at room temperature. The suspension was then washed in PBS and reincubated with goat antimouse IgG fluorescein isothiocyanate conjugate (Sigma Immunochemicals, Poole, UK) for 30 min at room temperature. The mixture was finally washed in PBS and resuspended in 1 ml PBS containing 1 mg/ml ribonuclease A (Sigma Chemical

Company) and 20 μ l propidium iodide (Sigma Chemical Company).

Flow cytometry

Prepared samples were analysed on a FACScan flow cytometer (Becton Dickinson, San Jose, California, USA). Data were analysed on 10000 events for each sample by measuring the number of positively labelled nuclei compared with the control, by setting computer-generated regions around each population of nuclei¹⁴ (the level of background nuclear staining being adjusted to be 1 per cent or less).

Statistical analysis

Population variables with normal distribution were assessed using Student's *t* test. Survival curves were constructed using the Kaplan-Meier product limit estimate¹⁵ and comparisons in survival curves made using the log rank test¹⁶. Survival data were analysed using JMP (SAS Institute, Cary, North Carolina, USA).

Results

Clinical data and pathology

Tumour samples were obtained from 30 female and 20 male patients, with a median age of 54.4 (range 20–93) years and median follow-up of 39 (range 10–183) months. Primary melanomas comprised nine superficial spreading malignant melanomas and five nodular melanomas, with a median thickness of 3.8 (range 1–7) mm. Metastatic melanomas included ten skin metastases and 26 nodal secondaries. Data on the primary tumour were available for all patients whose metastases were analysed, except for two patients who presented with secondary disease from an occult primary.

Expression of c-myc in primary and metastatic melanoma

Fig. 1 shows the DNA profiles and dot plots of c-myc expression for a typical diploid and aneuploid tumour.

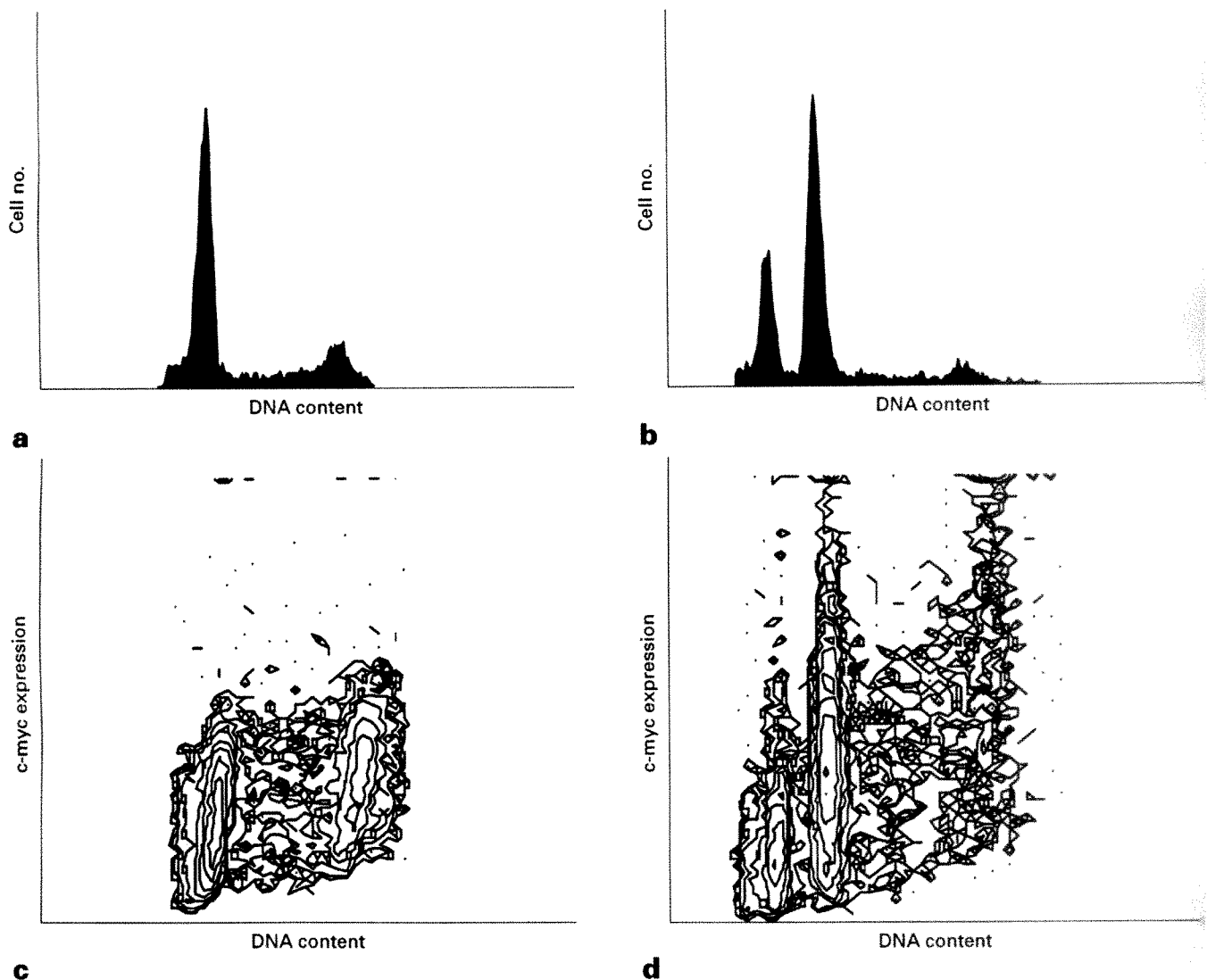


Fig. 1 DNA histograms of a diploid primary melanoma and b aneuploid nodal metastasis. Corresponding contour plots of c-myc positivity versus DNA content are shown for c the diploid primary melanoma and d the aneuploid nodal metastasis.

Seven of 14 primary tumours and 17 of the 36 metastases were aneuploid but there was no difference in the median c-myc positivity in diploid (47.7 (range 0–96.3) per cent) or aneuploid (41.3 (range 0–95.8) per cent) lesions.

Eleven of the 14 primary melanomas and 32 of 36 metastases were immunopositive for c-myc, representing 43 of 50 (86 per cent) melanomas assayed. The distribution of c-myc nuclear positivity exhibited a wide span of values between samples, ranging from 0 to 96.3 per cent. The overall median positivity of 45.9 per cent indicates that the oncoprotein was prevalent in relatively high amounts in the melanomas in this series.

The c-myc positivity for all primary melanomas was 44.8 (range 0–93.0) per cent. However, of more interest, oncoprotein positivity was found to vary with tumour thickness (Fig. 2); of the five primary melanomas less than 3.0 mm thick, two tumours were immunopositive, whereas all nine thick melanomas (greater than 3.0 mm) stained positively for c-myc. Nuclear positivity also varied with tumour thickness; median c-myc expression in melanomas less than 3.0 mm was 7.7 (range 0–22.1) per cent compared with 49.5 (20.9–93.0) per cent in tumours over 3.0 mm. This difference was highly significant ($P=0.008$). Consideration of oncoprotein levels in all specimens (i.e. including metastases) on the basis of primary tumour thickness emphasized the variation in positivity. Median c-myc positivity for melanomas less than 1.5 mm was 14.1

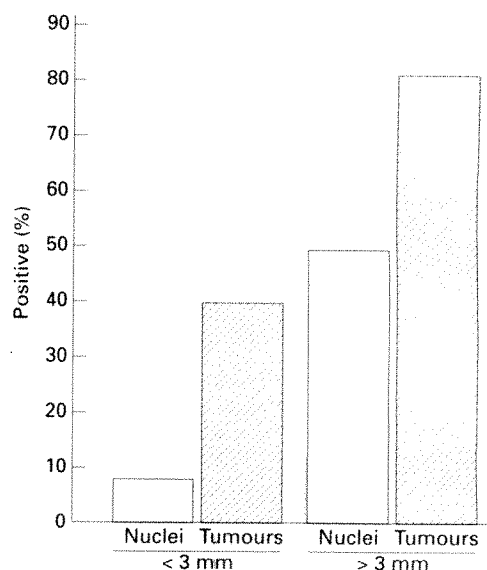


Fig. 2 Variation in c-myc expression with primary melanoma thickness. Bars represent the percentage of positive tumours and the median number of positive nuclei for tumours above and below 3 mm

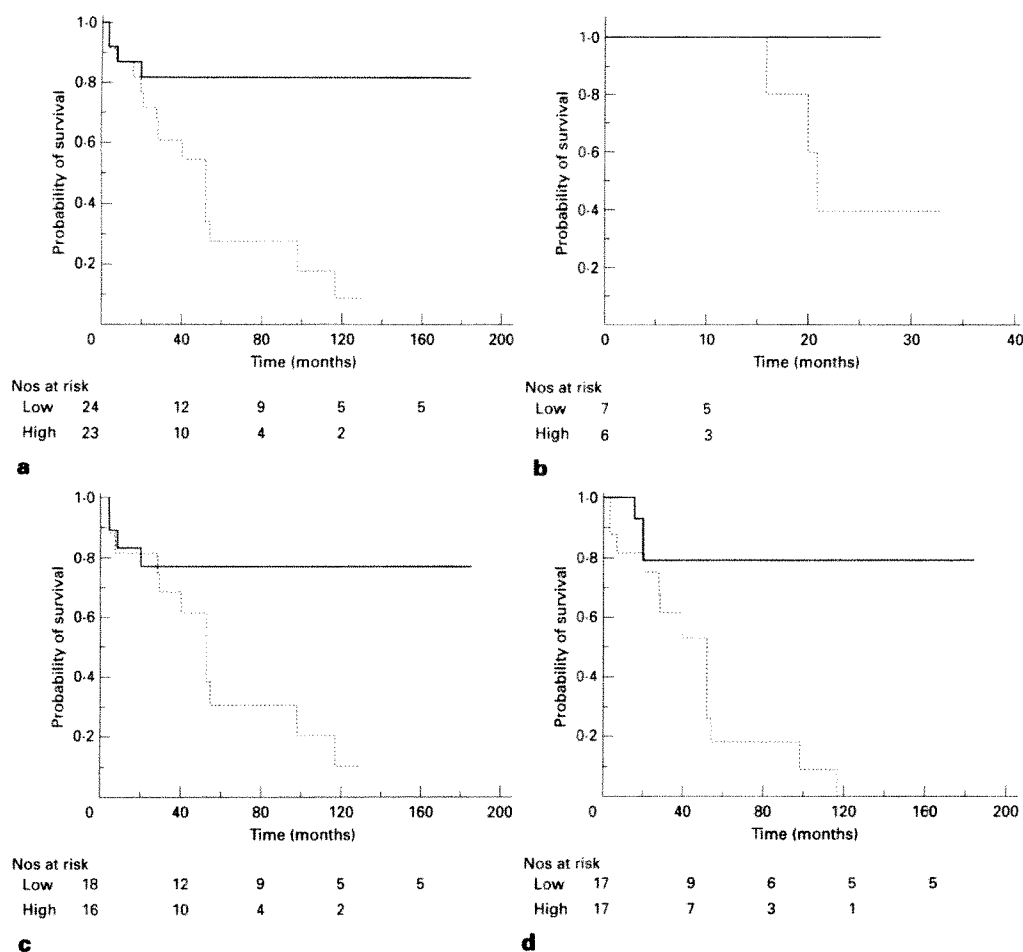


Fig. 3 Survival curves a for all patients (primary and metastatic tumours), b for those with primary tumours only, c for patients with locoregional disease and d for patients with primary tumours greater than 3 mm thick at presentation. All curves were stratified according to median c-myc positivity (—, below median; ---, above median) for each clinical group

Table 1 Expression of c-myc oncoprotein in primary and metastatic melanomas

Tumour type	Percentage of myc-positive tumours	Median percentage of myc-positive nuclei per tumour	P*
Primary melanoma			
≤ 3.0 mm	40.0	7.7	0.008
> 3.0 mm	100.0	49.5	
Secondary melanoma			
Nodal metastases	81.0	34.5	0.32
Skin metastases	80.0	70.7	
Ulceration			
Present	100.0	85.7	0.0001
Absent	83.0	29.3	
Mitotic figures			
≤ 5 per h.p.f.	84.0	61.7	0.1
> 5 per h.p.f.	95.0	33.1	
Disease-free interval (months)			
Below median	95.0	32.7	0.004
Above median	86.0	72.5	
Patient age (years)			
≤ 60	84.0	47.0	0.002
> 60	100.0	88.6	

h.p.f., High power fields. *Student's *t* test**Table 2** Variation in c-myc oncoprotein expression with location of the primary melanoma

	Head and neck	Torso	Lower limb
No. of melanomas	8	10	28
Median thickness of primary (mm)	4.6	3.8	3.6
Median c-myc positivity (%)	76.2 (20.8–96.3)	22.3 (0–61.7)	65.7 (0–95.8)

Values in parentheses are ranges

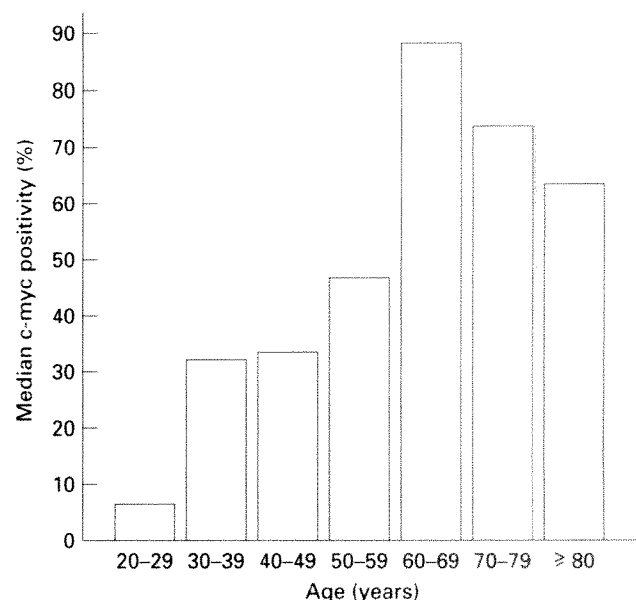
(range 0–94.8) per cent, and for tumours over 3.0 mm it was 56.8 per cent ($P=0.03$).

Of the 36 metastases analysed, 32 were c-myc positive. The overall nuclear positivity was 47.8 (range 0–96.3) per cent. Nodal and skin metastases appeared to have a considerable difference in median c-myc positivity but this was not statistically significant.

Expression of c-myc, disease progression and patient survival

Tumours with high c-myc expression (above median positivity) were associated with worse survival ($P=0.002$) when both primary and recurrent tumours were considered together (Fig. 3a). When primary tumours were considered in isolation (Fig. 3b), the influence of high c-myc expression did not quite reach significance ($P=0.08$) although this was probably because of the small number of patients. However, consideration of c-myc oncoprotein expression in the larger subgroup of patients with locoregional disease (Fig. 3c) revealed the level of expression to be a significant prognostic indicator ($P=0.008$).

Of particular importance, Fig. 3d shows that patients with thick primary melanomas (greater than 3.0 mm) and their metastases, with low c-myc oncoprotein content (below median positivity), were found to have a

**Fig. 4** Median c-myc positivity and age of the patient at time of excision biopsy

significantly improved survival compared with those whose melanomas expressed high levels of c-myc ($P=0.003$). At 10 years' follow-up, 16 of 18 patients presenting with thick melanomas with low c-myc content were still alive while all patients with raised c-myc protein levels had died.

Patient age and c-myc expression

Fig. 4 and Table 1 show the variation in c-myc expression with patient age. Expression was found to be greater in melanomas derived from patients above the median age and maximal in melanomas from patients aged 60 years and above ($P=0.002$).

Expression of c-myc and site of the primary or metastatic melanoma

Table 2 shows that primary melanomas and metastases arising on the head and neck had the highest c-myc oncoprotein content. This was significantly greater than the c-myc level detected in melanomas arising on the torso ($P=0.001$); c-myc positivity in melanomas on the lower limb was also significantly greater than oncoprotein levels found in melanomas on the torso ($P=0.01$), but not from the head and neck ($P=0.29$).

Histopathological parameters and c-myc expression

A strong association was observed between raised c-myc expression and the presence of ulceration in the primary melanoma ($P=0.0001$) (Table 1). In addition, a trend ($P=0.10$) was observed between c-myc expression and the presence of mitotic figures. Lymphocytic infiltration of the tumour was not found to be associated with c-myc level ($P=0.5$).

Disease-free interval and c-myc expression

The correlation between c-myc protein levels and survival was reflected in the association between this oncoprotein and the disease-free interval. The median c-myc positivity in patients with a low disease-free interval was 72.5 per cent compared with 32.7 per cent in patients with pro-

longed survival. This difference was highly significant ($P = 0.004$).

Discussion

The findings of this study suggest that c-myc oncoprotein may act as a prognostic marker for patients with melanoma when assayed in both primary disease and locoregional metastases. Multivariate analysis was performed on this series of patients using the Cox proportional hazards model¹⁷ and did identify c-myc as the most important independent prognostic indicator (data not shown). However, as the number of patients was small, particularly those with thinner lesions, emphasis has not been placed on these data; further analysis will be carried out in a larger series of tumours.

Using univariate analysis, raised oncoprotein expression was associated with decreased survival in all the groups studied. Furthermore, overexpression of c-myc was significantly associated with several established prognostic parameters for melanoma¹⁸ including primary tumour thickness, ulceration and disease-free interval.

The association between c-myc expression and primary tumour thickness has also been noted following immunohistochemical analysis¹³. Presently, patients presenting with primary melanomas in excess of 3 mm thick are classified as of uniform, poor, prognosis on the basis of this parameter alone¹⁸. However, consideration of c-myc positivity and outcome in thick (greater than 3 mm) melanomas suggests that oncoprotein overexpression may be independent of tumour thickness and further defines prognosis in patient groups currently defined as of uniform risk of progression. It would be of additional benefit if it were shown that c-myc also acted as a prognostic indicator in thin melanomas, as a proportion of these tumours will metastasize in spite of the favourable prognosis predicted by their thickness¹⁹; these studies are under way.

The observation that c-myc expression may predict tumour behaviour when assayed in patients with metastatic disease is noteworthy. Other than consideration of the number of nodes and extracapsular spread^{20,21}, no method is currently available to predict disease outcome in these patients despite the fact that their disease course may be highly variable^{18,22}. Future consideration of biological markers, such as c-myc oncoprotein, may aid patient management and stratify entrance into clinical studies.

The relationship between tumour site and c-myc oncoprotein content suggests that melanomas arising on sun-exposed sites may have higher c-myc oncoprotein expression. Melanomas from the head and neck and lower limb had significantly higher c-myc expression than melanomas developing on the torso. The underlying mechanism may involve ultraviolet radiation-induced genetic changes that result in either gene amplification or, more likely, post-translational modification involving the deregulation and activation of other oncogenes. The association between the site of melanomas and oncogene mutation has been reported for *ras* mutations which were found to be confined to melanomas arising in sun-exposed areas²³.

The observed association between c-myc overexpression and patient age is of particular interest. The rise in incidence of c-myc overexpression that accompanies age is consistent with the concept that cancer is a multistep

disorder but that melanoma may develop in younger patients by independent mechanisms. Tumours may arise following mutations of other oncogenes or due to the action of specific 'melanoma genes'²⁴. The recent identification of a potential melanoma suppressor gene on chromosome 9p21^{25,26} may suggest that deletion or mutation of such a gene is of relatively greater importance in the development of melanoma in younger patients.

This study found an association between c-myc positivity and a number of other markers of outcome, including tumour ulceration, the presence of mitotic figures and the disease-free interval. An association between c-myc positivity and increased mitotic figures was noted on immunohistochemical sections of melanomas¹³. The relationship between raised c-myc oncoprotein levels and decreased disease-free interval has been observed in head and neck squamous cell carcinomas¹² and in patients with breast cancer²⁷.

Overexpression of c-myc has been observed in a wide range of haematopoietic and solid cancers including those of the cervix, colon, head and neck, bladder, lung, breast and certain neurological tumours^{10, 12, 27, 28}, and thought principally to be due to gene amplification²⁹. However, it would appear that translocation and amplification only explain overexpression of c-myc in a small proportion of cases and the mechanism of overexpression in the majority remains unknown⁶.

The role of c-myc in the pathogenesis of melanoma has been studied to a very limited extent. Husain *et al.*³⁰ found c-myc mRNA to be raised between nine and 14 times in two metastatic cell lines compared with primary melanocytes and further suggested that c-myc overexpression was associated with anchorage independence and transfectability. A further study, investigating expression of 21 oncogenes in metastatic melanoma cell lines, found c-myc mRNA to be overexpressed in 16 of 18 cell lines, but only in the order of 1.5–3 times³¹.

The widespread increase of c-myc oncoprotein expression seen in this group of melanomas is consistent with the central role this gene is considered to have in growth control of both normal and malignant cells⁶. As a transcription factor, c-myc regulates the expression and activity of at least three major groups of genes: those controlling proliferation, differentiation and apoptosis⁷. Inappropriate raising of intranuclear oncoprotein levels would be expected to increase the number of cycling cells, resulting in a cell population that is predominantly proliferative and free of the opposing effects of differentiation³². This growth promoting effect may confer a selective advantage on certain tumours accounting for their relatively aggressive behaviour.

This study suggests an important prognostic role for c-myc in melanoma though the greatest benefit may lie in its potential as a specific therapeutic target.

Acknowledgements

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Non-invasive measurement of colonic blood flow distribution using laser Doppler imaging

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Background This study tested a prototype laser Doppler scanner for the measurement of human colonic blood flow.

Methods Blood flow distribution was assessed in human colon during operation in six controls and in six patients with inflammatory bowel disease undergoing colectomy. Image processing software analysed several hundred reading points, expressing average flow in perfusion units.

Results Blood flow in the colon was not significantly lower in the control group than in patients with inflammatory bowel disease (mean(s.e.m.) 297.8(24.5) versus 347.2(59.0) perfusion units, $P = 0.12$). Intestinal colonic mural blood supply was demonstrated up to a distance of 6 cm and ischaemia demarcation lines were identified before the onset of visible changes.

Conclusion This prototype laser Doppler flowscanner overcomes the previous limitations of laser Doppler flowmeters and may have many clinical and research applications.

Laser Doppler flowmetry is a non-invasive technique for measuring tissue blood flow^{1,2}. The technique involves measuring the Doppler frequency shift in light reflected from moving red blood cells in the tissue being studied. The technique suffers from a number of disadvantages which include: making measurements is tedious and sometimes unreliable³; it is susceptible to movement artefact and changes in orientation⁴ or probe geometry⁵; only small areas of tissue can be studied (3 mm²)⁶; and the probes have the potential to disturb local blood supply because of the contact pressure required to avoid optical dissociation⁷.

Despite these limitations, this method has been used to assess gastrointestinal blood flow in animals^{8–12} and humans^{13–17}. Results correlate well with tissue oxygen tension^{16,18} (without being affected by hypoxia¹⁹), isotope washout techniques (⁸⁵Kr washout¹⁰), hydrogen clearance^{20,21}, fluorescein flowmetry²², radioactive microsphere distribution²³ and electromagnetic flow probe measurements¹⁸. The depth of penetration is approximately 1 mm in skin^{24,25} and 6 mm in human colon²⁶, probably representing a composite or an integral of the transmural blood supply^{26,27}.

A new technique of laser Doppler scanning has recently been described²⁵. In this process, a laser beam remotely scans the surface of the biological tissue of interest (up to 0.5 m²) by means of a motor and mirror assembly. Blood flow is calculated by computer from the Doppler frequency and intensity of reflected light as the beam is moved along the colon. A colour-coded image of the distribution of blood flow is constructed and expressed in arbitrary perfusion units and can be presented as a contour map (Fig. 1). This study used a prototype laser Doppler scanner to measure and compare colonic blood flow distribution in 12 human volunteers (six controls, six with inflammatory bowel disease (IBD)) undergoing colectomy.

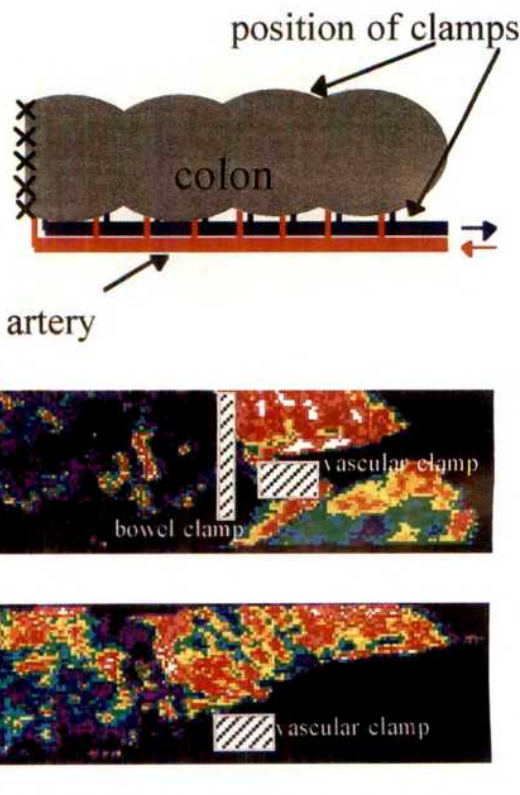


Fig. 1 Experimental arrangement to study the blood supply distribution (a) and the presence of mural blood supply in the colon. **b** Intestinal and vascular clamps *in situ*. **c** Intestinal clamp removed. Upon release of the intestinal clamp, any blood flow in the distal segment of the bowel could be due only to mural perfusion

Patients and methods

Twelve adult patients (eight men, median age 50 (range 24–79) years) were studied. Routine bowel preparation with Picolax (Ferring Pharmaceuticals, Feltham, UK) and Klean-prep

(Norgine, Harefield, UK) solution was instigated before operation. Six patients underwent colectomy for IBD and six for non-inflammatory conditions (rectal prolapse, one; carcinoma, five). Routine biochemical and haematological investigations were obtained within 48 h before operation and on the first postoperative day.

One patient was diabetic. Another patient, as a result of previous surgery, had only the ileocaecal artery supplying the right colon. These two patients were excluded from the numerical analysis of the blood flow data.

Anaesthesia was induced with thiopentone and maintained with a nitrous oxide–oxygen–isoflurane mixture. Intraoperative cardiorespiratory parameters were monitored continuously. After midline laparotomy the colon was mobilized routinely and delivered through the wound. A segment of colon approximately 25 cm long was prepared for the experiments in the following way: the colon and its blood supply were stapled and divided distally. The dissection in the mesentery was continued until all the accessory feeding vessels had been divided so that all blood supply came from a proximal feeding vessel (end artery). In two patients the bowel was not divided distally but was left in continuity having divided the distal blood supply (Fig. 1) to demonstrate mural blood flow (a bowel clamp could be applied to the distal colon to mimic the conditions in the other ten patients).

Before using the laser Doppler scanner, the bowel was surrounded with operative theatre drapes and all nearby metal objects were covered, in accordance with local safety protocols. The scanner was placed approximately 1 m above the patient and blood flow measurement was performed without any contact with the patient or the sterile operative field. Standard lighting conditions were maintained throughout the measurements to prevent interference from bright ambient light sources. The surface of the bowel was scanned using the laser Doppler scanner and then the mesentery was clamped and the scan repeated to establish a biological zero flow reading as, even at zero blood flow conditions, there is a persistent laser flux reading² possibly due to Brownian motion of the red blood cells and small random movements of the tissues.

Each scan took approximately 1.5 min. At the same time the intensity of reflected light (which measures tissue reflectance or 'sheen') was measured and stored along with the Doppler signal. These could be analysed separately. All intensity maps were inspected before blood flow analysis to ensure there were no abnormal areas due to reflection from metal instruments. Image processing software²⁵ was used to analyse areas of the colon on each scan. Each area contained several hundred reading points (pixels) and the average flow reading in perfusion units for each area was calculated. The scans were stored on a dedicated computer and analysed subsequently using specially designed software. The blood flow was averaged over the area of the bowel. The unpaired *t* test was used to compare the data.

Results

The preoperative haemoglobin level, haematocrit and mean corpuscular volume were within the normal range and there was no significant difference in these parameters after operation (Table 1).

Table 1 Preoperative and postoperative haematological parameters known to affect blood rheological characteristics

	Before operation	After operation	<i>P</i> *
Haemoglobin (g/dl)	11.9(2.14)	11.5(1.78)	0.40
Haematocrit	0.4(0.06)	0.4(0.05)	0.14
Mean corpuscular volume (fl)	81.1(7.42)	81.3(7.02)	0.61

Values are mean(s.d.). *Unpaired *t* test

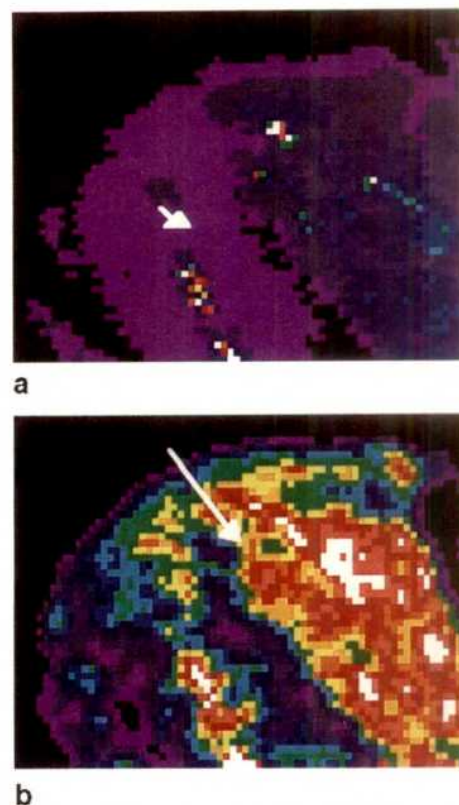


Fig. 2 Demonstration of devitalized bowel during mobilization. **a** Reflected light intensity and **b** Doppler flow data are measured and stored simultaneously, using the same colour scale. **a** Intensity data show that the bowel has lost its reflectance (purple zone, marked by arrowhead). **b** Doppler scan clearly shows the perfusion demarcation line (arrow) with normal flow on the right

In one patient the intensity scan showed that the colon was losing its reflectance during mobilization (Fig. 2a) and ischaemia was confirmed by the Doppler measurements (Fig. 2b). A new demarcation or resection line had to be adopted as suggested by the Doppler scan.

To demonstrate intestinal mural blood supply, the distal segment of the colon was rendered ischaemic by the application of mesenteric and intestinal cross-clamps. Upon release of the intestinal clamp, the distal segment of the colon was perfused with blood from the wall of the proximal segment up to a distance of at least 6 cm.

The mean(s.e.m.) biological zero value (i.e. the Doppler flow reading with all blood supply clamped) was 46.0(14.2) perfusion units, with no statistical difference between the two groups of patients (*P* = 0.88).

Mean(s.e.m.) blood flow in the colon was not significantly lower in the control group compared with that in patients with IBD (297.8(24.5) versus 347.2(59.0) perfusion units respectively, *P* = 0.12).

Discussion

The ability to measure tissue blood flow easily would be useful in both research and clinical practice. Laser Doppler techniques are the easiest to employ but have limitations, making them impractical for routine clinical use. They are tedious, time consuming and observer dependent^{3,28}.

Attempts to overcome these limitations and inter-observer variability include taking multiple readings over an extended time^{5,28} and modifications of the probe design. Examples of the latter include the development of a microprocessor-controlled moving arm to place the laser probe in precise coordinates²⁹, the use of multiple^{6,30} or hybrid probes incorporating a hydrogen electrode²¹ and, more recently, semiconductor designs³¹. These are all limited by the necessity to apply contact pressure to tissue.

The laser Doppler scanner²⁵ offers a fast, reliable and reproducible method of providing a tissue blood flow distribution map, at a cost comparable to that of currently available static devices. This technique does not suffer from significant movement artefacts, as the velocity of the laser beam and the time taken to estimate the data in one pixel are orders of magnitude faster than those of respiratory excursions and bowel peristalsis. Most importantly it is a no-contact method and therefore will not distort blood flow or sterility in the operating field. It should be possible to fix the final production model on to the theatre light. Two reports of this type of instrument have been made *in vitro* and in human skin^{32,33}. The measurements correlated well with ¹³³Xe washout blood flow measurements³³.

In the present study an evolution prototype was used, as reported by Essex and Byrne²⁵. The instrument was easy to use in the operating theatre, and statistical analysis functions incorporated in the software allowed averaging, histogram equalization and measurements of standard deviation to be made on raw data.

In the present study blood flow was higher in patients with IBD, although not significantly. This may reflect the handling of the normal tissue or the small number of patients studied. Some patients with inactive IBD were undergoing surgery for severe dysplasia. The study also demonstrated the presence of mural blood supply along the large intestine to a distance greater than the bowel circumference.

At zero blood flow conditions (e.g. with the tissue vasculature clamped) there is a persistent laser flux reading² or biological zero value amounting to approximately 15 per cent of the baseline flow value. Laser light of a different wavelength may contribute to a reduction of this artefact³⁰. This biological zero value was relatively small in well perfused tissues (5–10 per cent of baseline on a warm toe) but much larger in relatively ischaemic tissues³⁴ (59–83 per cent on a cold malleolus). The biological zero value of the laser Doppler flow scanner was similar in magnitude to that of the static instrument². As this parameter is a significant proportion of the resting laser Doppler flux measurement, it should be taken into account when reporting the results of blood flow measurements.

Numerous clinical and research applications for this instrument are apparent. The time-consuming studies on discrete point blood flow measurements on the intestine in animals^{8–12} and humans^{13–17} could be expanded by studying large segments, even the total length of the bowel. Studies of safe blood flow for colonic anastomosis and the effects of radiation can easily be undertaken. Segments of bowel affected by inflammatory disease might be identified by scanning the whole length of the intestine.

The laser Doppler flowscanner described here appears to have overcome some major disadvantages of previous laser Doppler flowmeters and can produce a map of the

spatial distribution of colonic blood flow non-invasively, quickly and easily.

Acknowledgements

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Experience with transcranial Doppler monitoring reduces the incidence of particulate embolization during carotid endarterectomy

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Background The aim of this study was to investigate whether the introduction of routine transcranial Doppler (TCD) ultrasonography during carotid endarterectomy reduces the incidence of microembolization by altering operative technique.

Methods The number and nature of microemboli detected during the first 75 consecutive carotid endarterectomies performed with TCD monitoring during 1992–1993 (group 1) were compared with those in a similar series of 75 consecutive patients undergoing carotid endarterectomy in 1995 (group 2), after substantial experience (210 patients) with TCD monitoring. Emboli were classified as either particulate or gaseous.

Results In patients with evidence of particulate emboli during the dissection phase of the operation, the total number of particulate emboli fell significantly in patients in group 2 ($P = 0.019$). Similarly, in patients in whom microembolization was detected on immediate opening of the shunt, the total number of microemboli also fell significantly in group 2 ($P = 0.003$). Overall, the median (95 per cent confidence interval) number of particulate emboli detected during the entire procedure fell significantly from 21 (16–29) in group 1 to 9 (7–14) in group 2 ($P = 0.0008$).

Conclusion TCD monitoring plays an important role in the training and quality control of carotid endarterectomy and helps significantly to reduce the amount of microembolization.

The principal cause of intraoperative neurological morbidity during carotid endarterectomy is particulate embolization. Fewer than 20 per cent of neurological events are attributable directly to haemodynamic factors alone¹. Until the advent of transcranial Doppler (TCD) ultrasonography the relative incidence of embolization during carotid endarterectomy was unknown. Recent studies have shown that TCD monitoring during carotid endarterectomy detects embolization at all stages of the operation^{2,3}, and can differentiate between gaseous and particulate emboli⁴. There remains scepticism about the clinical relevance of intraoperative microembolization and whether it is possible, or clinically relevant, to modify surgical technique to reduce its incidence.

Gaunt *et al.*⁵ showed that persistent particulate embolization during the dissection phase of carotid endarterectomy may be associated with a deterioration in cognitive function. Ackerstaff *et al.*⁶ showed a direct correlation between intraoperative particulate embolization and small lacunar infarcts seen on postoperative magnetic resonance imaging. The aim of the present study was to see whether the introduction of routine TCD monitoring has influenced operative technique sufficiently to reduce the incidence of intraoperative microembolization after a substantial 2-year learning curve.

The following changes to surgical technique had been made as a result of previous studies. (1) During dissection the surgeon was informed immediately of persistent particulate embolization, encouraging a more gentle dissection around the carotid bifurcation and, if necessary, premature clamping of the distal internal carotid artery. (2) On restoration of flow after shunt insertion there was prolonged flushing of the shunt before insertion into the

internal carotid artery. (3) There was less manipulation of the shunt or shunt repositioning if microembolization was persistent during the endarterectomy while the shunt was in place. (4) Prolonged backbleeding was instituted at final restoration of flow. (5) Where a Dacron (Du Pont, Stevenage, UK) patch was used, it was presoaked in saline to release small gaseous emboli trapped within the woven material.

Patients and methods

The number and nature of intracranial microemboli detected using TCD ultrasonography during 75 consecutive carotid endarterectomies in 1992–1993 were compared with those in a similar series of 75 consecutive patients undergoing carotid endarterectomy in 1995. All 150 patient data recordings were carried out using the same equipment and were analysed identically by one observer. Comparisons for age, sex, degree of stenosis, predominant presenting symptom, patch type, diabetic status, smoking habits and hypertension are shown in *Table 1*. Preoperative computed tomography was not used. Plaque morphology classification from B-mode ultrasonography was performed in patients in group 1 but was found to be of little clinical value and was therefore discontinued in 1994⁷.

The operations were performed by a consultant (P.R.F.B., A.R.N. and N.J.M.L.) or by a higher surgical trainee under supervision. In group 1, 24 operations were performed by a higher surgical trainee, compared with 39 in group 2. Distinguishing between gaseous and particulate emboli was important, as particulate embolization has the potential to cause more substantial clinical sequelae; this distinction was effected with a new method of analysing Doppler ultrasound signals called Wigner analysis rather than the more conventional fast Fourier transform analysis⁴. All 150 operations were performed under normotensive normocarbic general anaesthesia using continuous TCD monitoring. Mean middle cerebral artery velocity was maintained at least at 15 cm/s during all phases of the operation⁸. Intravenous heparinization (5000 units) was given

Table 1 Clinical data

	Group 1*	Group 2†
Median (i.q.r.) age (years)	68 (60–72)	68 (63–72)
Median (i.q.r.) percentage stenosis	80 (75–85)	80 (75–90)
Sex ratio (F:M)	23:52	25:50
Carotid patch type		
Dacron	41	53
Vein	30	20
Vein graft	0	2
PTFE	2	0
No patch	2	0
Hypertension		
Yes	41	44
No	34	31
Smoking		
Yes	13	19
Past	40	39
No	22	17
Diabetes		
Yes	11	8
No	64	67
Predominant presenting symptom		
Stroke	26	23
TIA	44	40
Amaurosis fugax	5	4
Asymptomatic	0	8

*The first 75 patients who had transcranial Doppler ultrasonography; †75 patients treated in 1995. i.q.r., Interquartile range; PTFE, polytetrafluoroethylene; TIA, transient ischaemic attack

immediately before cross-clamping of the carotid artery and was not reversed at the end of the procedure. A Pruitt–Inahara shunt was used routinely. The endarterectomy was done through a longitudinal arteriotomy and closed with either a vein or prosthetic patch. Before final restoration of flow the endarterectomy site was visualized with an angioscope to exclude any residual thrombus or intimal flaps. A patient who recovered from anaesthesia with a new neurological deficit was deemed to have suffered an intraoperative stroke and this was correlated directly with patterns of operative particulate embolization.

Continuous TCD monitoring (PCDop 842; SciMed, Bristol, UK) was used throughout the procedure with the ipsilateral middle cerebral artery insonated at a depth between 4.5 and 5.5 cm. After anaesthetic induction the probe was positioned with the aid of an elasticated headband and angle-adjustable probe holder, and protected from dislodgement with a metal semicircular headguard fixed securely to the operating table. The Doppler signal was displayed on a monitor during surgery and was audible in the theatre; it was recorded on to digital audiotape for further off-line analysis. The operation was subdivided into six stages: dissection (skin incision to internal carotid clamping); shunt opening (internal carotid clamping to 1 min after shunt opening); during shunting (1 min after shunt opening to shunt removal); external carotid artery flow restoration (external carotid flow restoration to immediately before restoration of flow to the internal carotid); internal carotid artery flow restoration (1 min after flow restoration or until no further surgical manipulation to the carotid arteries); and skin closure (remainder of the procedure).

The number and nature of each embolic signal detected during each stage of the operation were evaluated. Emboli were detected according to standard criteria as high-intensity transient signals producing distinctive audible 'chirps'. Generally embolic signals are contained within the background Doppler blood signal (Fig. 1a); however, signals from gaseous emboli backscatter a higher proportion of the incident ultrasound and frequently produce a bidirectional signal covering the entire vertical screen display. This is due to overload of the Doppler

system and has been described as embolus overload artefact¹⁰ or extraspectral aliasing¹¹. During off-line analysis, once an embolic signal was isolated, the Wigner analyser allowed a highly magnified image to be visualized, permitting more accurate measurement of embolic duration and velocity (Fig. 1b). Emboli were classified as gaseous or particulate according to sample volume length (the length of artery over which an embolic signal is detectable), which was calculated from the product of velocity and duration. A threshold value for the sample volume length was set at 1.28 cm, whereby all embolic signals below this threshold were deemed to be particulate and all those above were defined as gaseous bubbles. Previous work has shown this method of differentiation to be highly sensitive and specific¹. During the dissection and recovery phases of the operation all embolic signals were particulate because, at these two stages, the closed arterial system prohibited the introduction of air. A small number of patients experienced a shower of embolic signals either during shunt opening or on restoration of flow to the internal and external carotid arteries after completion of the endarterectomy. Although the Wigner analyser was able to identify discrete events within some of the showers when visualized in the highest resolution mode, some showers revealed many overlapping embolic signals that could not be analysed accurately. In these cases the entire duration of each shower was taken as an approximate indicator of the number of emboli present.

Statistical analysis

The data were not distributed normally (Filliben's test)¹² and thus non-parametric tests of statistical analysis were used (Mann–Whitney *U* test). Statistical significance was assumed at $P \leq 0.05$.

Results

Intraoperative microembolization was detected in 74 (99 per cent) of the patients in group 1 and in 72 (96 per cent) of those in group 2. Particulate embolization during the dissection phase was apparent in 29 patients (39 per cent) in group 1 and 22 (29 per cent) in group 2 (Table 2).

In patients who had emboli the median (95 per cent confidence interval (c.i.)) number of particulate emboli detected during dissection was 10 (4–14) in group 1 falling to 2 (1–5) in group 2 ($P = 0.019$) (Table 3). A statistically significant reduction in microembolization was also achieved on shunt opening ($P = 0.003$) with the median (95 per cent c.i.) number of emboli for group 1 being 7 (5–9) compared with 4 (3–5) for group 2. Two patients in group 1 had embolic showers on shunt opening compared with three in group 2. The total duration for the two groups was 3.4 and 3.1 s respectively. Only one patient in group 1 had a shower of emboli (0.9 s) on restoration of flow to the external carotid artery, compared with five in group 2 (total duration 9.0 s).

Table 2 Number of patients with one or more emboli detected during each operative phase

Operative phase	Group 1 (<i>n</i> = 75)	Group 2 (<i>n</i> = 75)
Dissection	29	22
Shunt opening	58	49
During shunting	47	42
ECA flow restoration	29	34
ICA flow restoration	68	65
Skin closure	8	3

ECA, external carotid artery; ICA, internal carotid artery

Table 3 Emboli detected at each operative stage

Operative phase	Group 1 (n = 75)	Group 2 (n = 75)	P*
Dissection	10 (4–14)	2 (1–5)	0.019
Shunt opening	7 (5–9)	4 (3–5)	0.003
During shunting	7 (4–11)	4 (2–7)	0.138
ECA flow restoration	8 (5–12)	4 (3–7)	0.078
ICA flow restoration	19 (14–27)	16 (12–21)	0.75
Skin closure	111 (19–231)	Sample too small	—
Duration of shower (s)	1.2 (0.9–6.4)	1.5 (0.8–2.2)	0.60
Total particulate	21 (16–29)	9 (7–14)	0.0008
Total gaseous	18 (14–24)	15 (11–19)	0.13
Total emboli	43 (33–55)	25 (19–31)	0.002

Values are median (95 per cent confidence interval). ECA, external carotid artery; ICA, internal carotid artery. *Mann–Whitney *U* test

Embolic showers on restoration of flow to the internal carotid artery occurred in nine patients in both groups, with the duration in group 1 totalling 30.3 s compared with 9.4 s in group 2. As a whole, 11 and 14 patients had evidence of embolic showers during endarterectomy in groups 1 and 2 respectively.

There was no significant difference in the reduction in the number of particulate emboli or the overall reduction in the total number of microembolizations between oper-

Table 4 Number of emboli detected for each group of patients and according to seniority of the operating surgeon

Surgeon	Embolus type	No. of emboli		P*
		Group 1 (n = 75)	Group 2 (n = 75)	
Higher surgical trainee	Gaseous	16 (9–28)	14 (9–19)	0.51
	Particulate	24 (14–34)	10 (6–18)	0.026
	Total	43 (28–68)	23 (16–34)	0.042
Consultant	Gaseous	19 (14–27)	16 (10–23)	0.32
	Particulate	19 (13–30)	8 (5–14)	0.008
	Total	44 (30–57)	26 (19–36)	0.048

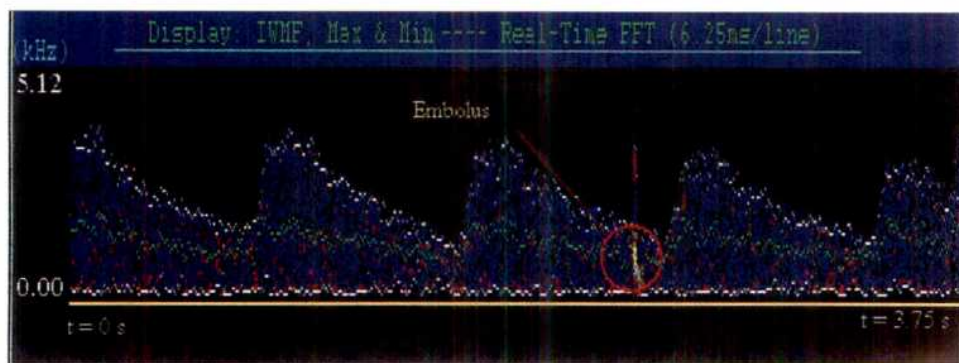
Values are median (95 per cent confidence interval). *Mann–Whitney *U* test

ations performed by a higher surgical trainee and those performed by a consultant (Table 4).

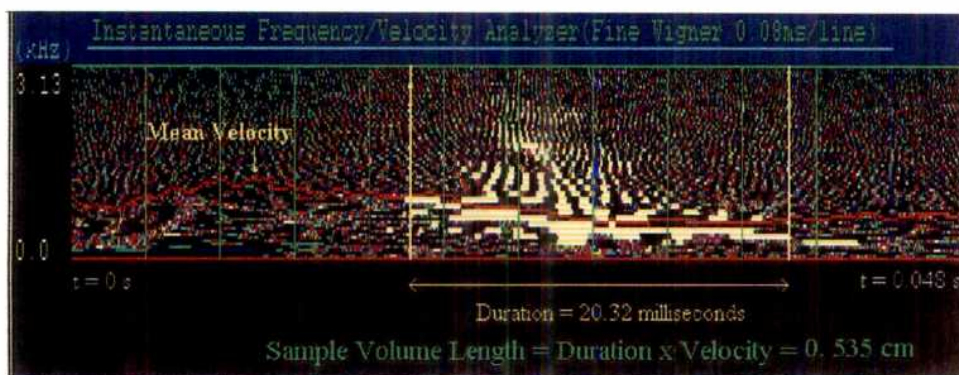
One patient (1 per cent) in group 1 recovered from anaesthesia with a new and persistent neurological deficit (intraoperative). This patient had 315 particulate emboli detected during skin closure and, when re-explored, was found to have suffered an on-table carotid occlusion. No patient in group 2 recovered from anaesthesia with any new intraoperative neurological deficit.

Discussion

Particulate microembolization correlates with cognitive deficits and small infarcts detected on magnetic resonance



a



b

Fig. 1 **a** Conventional Doppler spectrum with an embolic signal of extremely short duration visible in bright yellow and circled in red. The timescale along the horizontal axis is 3.75 s. **b** The same embolic signal highly magnified using the Wigner analyser. The timescale on this axis is only 48 ms. The sample volume length (0.53 cm) is calculated from the lower trace from the product of embolus velocity (26.3 cm/s) and embolus duration (20.3 ms)

scans^{5,6}. It was hoped, therefore, that this type of embolization could be reduced with TCD ultrasonography. Before operating on the 75 patients in group 2, 210 carotid endarterectomies had been done using TCD monitoring. This study showed that, for subsequent operations, the number of particulate emboli detected during dissection was reduced significantly ($P=0.019$) as a result of altering operative technique. Overall, the total number of particulate emboli detected during the entire procedure was reduced significantly in group 2 ($P=0.0008$).

Microembolization is extremely common during carotid endarterectomy and was detected in 97 per cent of patients in this study. In the majority, the emboli were due to gas bubbles entering the arterial system at times of shunt insertion and at final restoration of flow to both the external and internal carotid arteries. Gaseous emboli are common but do not have any effect on cognitive function or clinical outcome, except in the case of gross gaseous emboli due to shunt complications⁴. Lengthy showers of presumed gaseous emboli could contain small particulate debris and therefore it is preferable to minimize gaseous emboli introduced at times of shunt opening and flow restoration. In this study the number of patients with evidence of embolic showers did not decrease significantly but the maximum (median (95 per cent c.i.)) duration was only 2.9 (1.5 (0.8–2.2)) s in group 2 compared with 11.8 (1.2 (0.9–6.4)) s in group 1 ($P=0.60$). The reduction in the duration of individual showers was attributed to the surgeon increasing the amount of flushing through the shunt before insertion and prolonged back-venting before final restoration of flow.

It is not only the number of particulate emboli that is a risk factor for clinical complications following surgery but also the frequency with which emboli occur. There is evidence that inadequate collateral cerebral circulation and the presence of existing cerebral infarcts reduces the amount of particulate embolization, which may have clinical effects¹¹. In vulnerable patients, the margin for technical error is reduced¹³.

This study has shown that surgical technique can be influenced by intraoperative TCD monitoring. In particular, careful dissection has significantly reduced the amount of particulate embolization and thus reduced the risk of cognitive deficit. A randomized trial of TCD monitoring would be difficult to carry out because vascular surgeons have already adapted their technique. TCD ultrasonography plays an important role in the quality control of carotid endarterectomy and provides a useful teaching input for surgeons in training.

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Popliteal vein reflux reduces the healing of chronic venous ulcer

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Background The relationship between deep and superficial venous reflux and healing of venous ulceration by non-operative compression therapy has not been studied previously.

Methods A total of 155 patients with chronic venous ulcers underwent duplex ultrasonography before treatment with compression bandaging at a hospital-based venous clinic.

Results At 24 weeks, 104 (67 per cent) of ulcers had healed. There was no significant difference in the pattern of either deep or superficial venous reflux between healed and non-healed ulcers except with respect to the popliteal vein. In healed ulcers, 39 scans (38 per cent) indicated competence of the above-knee popliteal vein compared with five (10 per cent) in the non-healing group ($P < 0.001$, χ^2 test). Similarly, 43 scans (42 per cent) showed below-knee popliteal vein competence in the healed ulcers compared with only five (10 per cent) performed in legs remaining ulcerated ($P < 0.001$, χ^2 test).

Conclusion Popliteal vein incompetence is an indicator of poor response to compression therapy for venous ulceration.

Venous ulceration has a prevalence of 1–2 per cent and is estimated to cost the UK National Health Service £300–600 million per year¹. Venous reflux is the primary cause of chronic venous ulceration², whereas venous outflow obstruction is a factor in 5–12 per cent of cases^{3–5}. The relative importance of reflux at different sites within the deep and superficial venous systems remains unclear. In 10–50 per cent of patients with venous ulceration, incompetence is limited to the superficial venous system alone⁶. In addition, incompetent communicating veins are found in 70–100 per cent⁷. Although there are patients whose venous ulceration will respond to perforator and saphenous ligation alone⁸, this does not lead to permanent ulcer healing in the presence of deep venous reflux^{9,10}.

Several studies have shown deep venous reflux to be an importance cause of ulceration^{3,4,7}. McEnroe *et al.*³ demonstrated that 72 per cent of patients with venous ulceration had deep venous insufficiency alone and 15 per cent had a combination of deep and superficial insufficiency. Raju and Fredericks⁴ detected pure deep vein reflux in 75–88 per cent of legs in patients with post-thrombotic venous ulceration. No patient had superficial venous insufficiency alone and it was suggested that communicating and superficial reflux were secondary phenomena⁴.

Duplex ultrasonography allows non-invasive assessment of individual veins and is more sensitive than phlebography¹¹. Hanrahan *et al.*¹² used duplex imaging to demonstrate several combinations of venous incompetence involving superficial, communicating and deep veins in 95 patients with venous ulceration. The aim of the present study was to determine the relationship between anatomical patterns of venous reflux and ulcer healing in response to ambulatory compression therapy.

Patients and methods

The study population comprised 155 patients with chronic venous ulceration who presented to one of two hospital-based clinics in the Lothian and Forth Valley Leg Ulcer Study Project during the course of a two-centre clinical trial with factorial design. The study was approved by Lothian Health, and informed written consent was obtained.

All patients were treated with compression therapy (randomly allocated to either elastic single-layer or multilayer bandaging) for 6 months and healing was assessed at monthly intervals. In addition, patients were treated with one of two dressings by random allocation: knitted viscose or hydrocolloid. They were also randomized to oxpentifylline 400 mg three times a day or placebo. Patients with evidence of arterial disease (ankle:brachial pressure index less than 0.8), diabetes, and clinical or serological evidence of connective tissue disease (positive for rheumatoid factor or antinuclear factor) were excluded.

Before treatment all patients underwent duplex ultrasonography which was performed by a consultant radiologist (P.L.A.) using an Acuscan 125 colour flow duplex scanner (Acuson, Mountain View, California, USA). Duplex imaging was performed at ten predesignated sites: common femoral, superficial femoral, above- and below-knee popliteal, peroneal, anterior and posterior tibial, long saphenous (origin and mid thigh segments) and short saphenous veins. Patients were examined standing using manual calf compression and the Valsalva manoeuvre. Venous reflux was defined¹³ as the presence of reversed flow lasting longer than 0.5 s.

Results were analysed by the χ^2 test with Yates' correction, stepwise linear logistic regression analysis and Kaplan–Meier life-table analysis.

Results

The male:female ratio was 1.8:1, with a median age of 69 (range 34–88) years. The median maximum ulcer diameter was 29 (range 10–140) mm, and the majority (143) were located in the gaiter region. The median duration of the current ulcer was 5 (range 2–144) months,

and the median number of previous episodes of ulceration was 2 (range 1–20). Twenty-four patients had a previous history of deep venous thrombosis.

At 24 weeks, 104 (67 per cent) of ulcers had healed. There was no significant relationship between the type of dressing and bandages used and the rate of healing in the 104 patients studied^{14,15}. In addition, oxpentifylline compared with placebo had no effect on healing¹⁶. There was no significant difference in the pattern of deep or superficial venous reflux between healed and non-healed ulcers at any site except the popliteal vein (Table 1). In healed ulcers, 39 scans (38 per cent) indicated competence of the above-knee popliteal vein compared with five (10 per cent) in the non-healing group ($P < 0.001$, χ^2 test with Yates' correction; sensitivity 90 per cent, specificity 38 per cent, positive predictive value 42 per cent, negative predictive value 89 per cent) (Fig. 1). Similarly, 44 scans (43 per cent) showed below-knee popliteal vein competence in healed ulcers compared with five (10 per cent) performed in legs remaining ulcerated ($P < 0.001$, χ^2 test with Yates' correction; sensitivity 90 per cent, specificity 43 per cent, positive predictive value 44 per cent, negative predictive value 90 per cent) (Fig. 2).

Combining the duplex findings in the above- and below-knee popliteal segments resulted in a stronger association with non-healing. Four (10 per cent) of 42 patients with competent and 45 (44 per cent) of 103 with incompetent above- and below-knee popliteal vein failed to heal ($P < 0.001$, χ^2 test; sensitivity 92 per cent, specificity 40 per cent, positive predictive value 44 per cent, negative

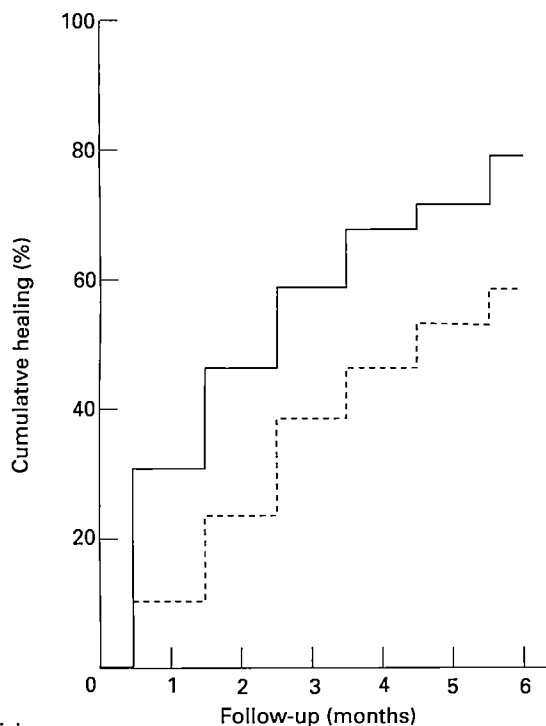
Table 1 Results of duplex imaging at selected anatomical sites

Venous segment	Non-informative scan	Healed: no reflux*	Healed: reflux*	P†
Long saphenous (origin)	23	18 of 24	70 of 108	0.47
Long saphenous (mid thigh)	18	17 of 21	75 of 116	0.23
Short saphenous	10	28 of 35	69 of 110	0.09
Common femoral	3	21 of 25	80 of 127	0.07
Superficial femoral	4	35 of 53	65 of 98	0.89
Proximal popliteal	1	39 of 44	64 of 110	0.0006
Distal popliteal	1	44 of 49	59 of 105	0.0008
Posterior tibial	24	36 of 52	51 of 79	0.72
Anterior tibial	34	69 of 98	13 of 23	0.49
Peroneal	48	37 of 54	34 of 53	0.78

*Values are the number healed of the total number with or without reflux. † χ^2 test

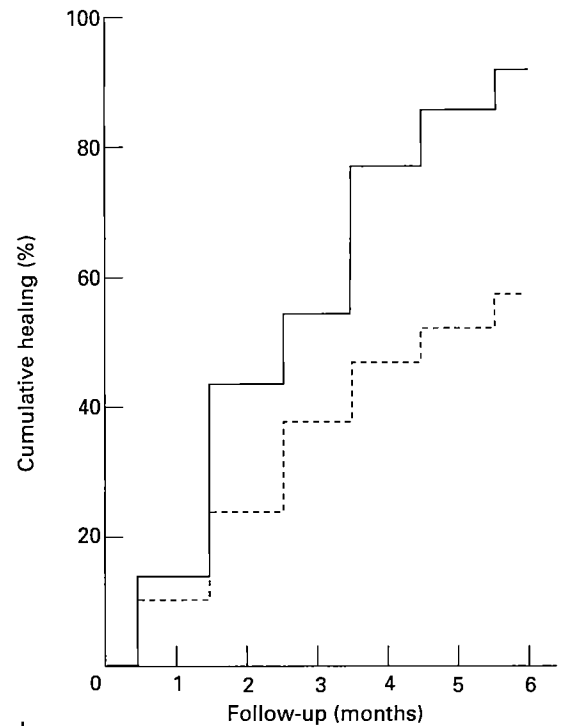
predictive value 91 per cent). If the definition of reflux was taken to be greater than or equal to 1 s of reverse flow, the findings were similar.

The only significant difference between the healed and non-healed group remained with respect to the popliteal segment. Stepwise linear logistic analysis confirmed these findings but, in addition, showed a significantly improved rate of healing in patients with superficial femoral segment incompetence. This was not significant on



No. at risk
Competent 44 38 25 16 10 7 5
Incompetent 110 100 84 67 59 53 46

Fig. 1 Kaplan-Meier life-table analysis showing percentage cumulative healing over a 6-month period in patients with competent (—) and incompetent (---) above-knee popliteal valves



No. at risk
Competent 49 42 28 18 12 8 5
Incompetent 105 96 81 65 57 52 46

Fig. 2 Kaplan-Meier life-table analysis showing percentage cumulative healing over a 6-month period in patients with competent (—) and incompetent (---) below-knee popliteal valves

univariate analysis (Table 1) and appears physiologically implausible. This statistical finding has, therefore, been attributed to chance.

Discussion

This study was conducted within the confines of a randomized clinical trial (which has been reported elsewhere^{14–16}). Because the patients were being assessed meticulously, treatment was standardized by protocol and the duplex scans were all carried out by a single expert observer. The relationship between healing response and pattern of reflux was statistically independent of the treatment modalities, and indeed the fact that therapies were randomized in a factorial design strengthens the statistical power of the observations.

This prospective study has demonstrated that popliteal vein incompetence is strongly associated with delayed and non-healing of venous ulcers. This accords with previous publications which have emphasized the importance of the popliteal segment in the pathogenesis of venous ulceration^{7,17}. It has been suggested that a competent popliteal vein valve acts as a 'gatekeeper' for the calf muscle pump^{18–20}. Popliteal vein reflux was the most important factor in determining the ambulatory venous pressure in post-thrombotic limbs²¹. Shull *et al.*²¹ found that ulceration did not occur unless the popliteal valve was incompetent on Doppler examination. In the present study, 42 patients with venous ulceration had a competent popliteal segment but the incidence of previous deep venous thrombosis was low. The differing results may be due to the fact that duplex imaging was used in the present study. When Doppler ultrasonography is used in the popliteal fossa it is difficult to determine which vein is being assessed¹³. Duplex ultrasonography can assess individual vein valves and has advantages over descending venography, which underestimates reflux, especially in the presence of competent proximal valves¹¹. In agreement with previous reports²², tibial vein reflux was not well demonstrated by duplex scanning in this study (Table 1).

All patients with chronic venous ulceration ideally should undergo an initial duplex scan of the venous system. Graduated compression therapy and elevation at rest remain the mainstay of treatment and are successful in most patients. An improved understanding of the calf muscle pump, vein valve function and pathophysiological flow may improve patient selection for both superficial and deep venous surgery.

Acknowledgements

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Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma

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Background The possible immunosuppressive effect of blood transfusion and its influence on survival after surgery for cancer makes it worthwhile to seek methods to avoid transfusion wherever possible. Patients with right-sided colonic cancer are frequently anaemic. Such patients were entered into a study that employed erythropoietin to avoid homologous transfusion.

Methods In a prospectively randomized double-blind placebo-controlled multicentre trial, patients with moderate anaemia (haemoglobin concentration greater than 8.5 g/dl and less than or equal to 13.5 g/dl) presenting with right-sided colonic cancer and scheduled for hemicolectomy were treated with recombinant human erythropoietin (epoetin β) 20 000 units/day subcutaneously or placebo for at least 10 days over the operative period.

Results Perioperative treatment with epoetin β was well tolerated and there were no significant differences in morbidity and mortality. Following hemicolectomy, median cumulative blood loss in the two groups was similar (epoetin β 440 ml *versus* placebo 345 ml). Sixteen (33 per cent) of 48 patients treated with epoetin β and 15 (28 per cent) of 54 in the placebo group received perioperative blood transfusions (*P* not significant). The increase in reticulocyte count between baseline and the last preoperative value was more pronounced in the epoetin β group than in those receiving placebo (*P* = 0.036).

Conclusion Despite the perioperative administration of 20 000 units erythropoietin per day for at least 10 days, it was not possible to reduce the intraoperative and postoperative transfusion need. None the less, a positive change in the haematological variables of treated patients was clearly discernible. The negative result may be due to the short treatment interval and to iron deficiency, which was present in the majority of patients. The general change of attitude towards allogeneic blood transfusion is demonstrated by the overall low frequency of blood transfusion in this study.

In the operative treatment of malignant tumours, homologous blood transfusions often become necessary. The frequency of transfusion depends on the tumour type and size. For colorectal cancer the reported transfusion frequencies are between 45 and 86 per cent^{1–3}.

The principal problems of homologous blood transfusion are the transmission of infection, which cannot be ruled out even with modern serological methods, and immunosuppression. Much attention has been paid in recent years to a possible adverse effect of perioperative blood transfusion on the outcome of patients with malignant tumours^{4–7}.

Currently used alternatives to homologous blood transfusion are predeposit blood donation, haemodilution and intraoperative autotransfusion with a cell saver. In patients with tumours, however, the use of a cell saver is questionable because of the risk of retransfusion of tumour cells. It has been demonstrated that tumour cells can survive in the mechanically processed blood unit^{8,9}. As tumour patients usually are scheduled for operation shortly after diagnosis, predeposit donation can be applied to only a limited degree in these patients.

Clinical studies with recombinant human erythropoietin (epoetin β) in orthopaedic patients have shown that it is

possible to increase the number of autologous blood donations before operation and thus to decrease the need for homologous blood transfusion^{10,11}. The benefit of epoetin β in tumour-associated anaemia is currently being investigated^{12–14}.

Patients with right-sided colonic cancer are more frequently anaemic than those with colorectal tumours at other locations. As a large proportion of these patients could be expected to be transfused over the operative period, they were used for this study of preoperative treatment with erythropoietin.

Patients and methods

Study objective

The primary objective of the study was to analyse the efficacy of the perioperative subcutaneous administration of 20 000 units per day of epoetin β in reducing the requirement for blood transfusion in anaemic patients undergoing right hemicolectomy for colonic cancer. Secondary objectives were the investigation of the efficacy of epoetin in reducing the time needed after operation to achieve 95 per cent of the individual baseline haemoglobin value, and to assess the clinical tolerability of epoetin β in these patients. The baseline haemoglobin concentration was defined as the value at study entry. The time taken (in days) after operation for haemoglobin concentration to reach 95 per cent of the baseline level was noted.

Study protocol

Patients were considered eligible for the study if they fulfilled the following criteria: cancer of the colon scheduled for right hemicolectomy, age over 35 years, anaemia with a haemoglobin concentration at first visit greater than 8.5 g/dl and less than or equal to 13.5 g/dl, and no preoperative blood transfusion. Exclusion criteria were cardiopulmonary disease, hypertension not controlled medically, metabolic or endocrine disorders, and a second malignancy other than *in situ* cervical cancer. Informed written consent was obtained and patients were randomized to receive either epoetin β 20000 units subcutaneously or placebo for a minimum of 5 (maximum 10) preoperative days and until postoperative day 4. The indication for transfusion was set at a haemoglobin level of 7.5 g/dl or lower. Oral iron supplementation was carried out in case of iron deficiency, and on postoperative day 1 all patients were given 40 mg iron sulphate intravenously. The last follow-up visit was 3 months after operation. The study protocol was approved by the ethics committees of the University of Heidelberg and the Free University of Berlin.

Sample size

According to the study protocol it was planned to randomize a total of 212 patients and to perform an interim analysis (two-tailed type I error of 1 per cent or less) when results from 50 per cent of the patients to be randomized were available. For the final analysis (two-tailed type I error of 4 per cent or less), two groups of 90 patients (180 in total) were to be evaluable to detect a reduction in transfusion need from 50 per cent in the control group to 25 per cent in the epoetin β treatment group with a power of 90 per cent. The assumed transfusion need of 50 per cent in the placebo group was based on retrospective analysis of 546 patients with colorectal carcinoma at the Surgical Department of the University of Heidelberg.

Statistical analysis

After enrolment of 109 patients, recruitment was stopped to perform the planned interim analysis presented here. Further patients were not recruited because epoetin β was found not to have an effect with respect to avoidance of homologous blood transfusion.

Fisher's exact test was used to compare the percentages of transfused patients in both treatment groups (primary endpoint) and to analyse further dichotomous variables. The time between the day of operation and the day of reaching 95 per cent of the baseline haemoglobin value was analysed with the Wilcoxon rank sum test. This test was also used for all further ordinal scaled and continuous variables with non-normal distribution. Multiple logistic regression analyses were performed to search for prog-

nostic factors for transfusion need. To facilitate interpretation of the results of the logistic regression, quantitative data with continuous distributions were stratified using appropriate cut-off levels (e.g. age 70 years or less and more than 70 years). Results are expressed as frequency (percentage), median and interquartile range, or odds ratio (2.5 and 97.5 per cent confidence limits of the odds ratio), as appropriate. Two-tailed tests were used throughout.

Patients

A total of 109 patients were enrolled at 16 participating hospitals between February 1992 and August 1993. Seven patients (four receiving epoetin β and three receiving placebo) were excluded from analysis: two patients receiving epoetin β dropped out because of adverse events before surgery, two in the placebo group were transfused before operation, in two receiving epoetin β colonic carcinoma was not confirmed at operation and hemicolectomy was not carried out, and in one patient in the placebo group only palliative ileotransverse colostomy was performed owing to irresectable carcinoma. One patient in the placebo group in whom subtotal colectomy was performed was included in the analysis. This left 102 patients (48 receiving epoetin β and 54 receiving placebo) for analysis of treatment efficacy.

Table 1 presents demographic information and baseline characteristics of the two study groups. There were no differences in sex ratio between the two groups. The median age in the epoetin β group (71 years) was significantly higher than that in the placebo group (67 years). There were no significant differences in calculated blood volume, baseline values of haematological variables and serum ferritin concentration between the study groups. Serum iron and transferrin saturation values were significantly lower in patients receiving epoetin β than in those having placebo. There were no significant differences with respect to the calculated blood volume. Iron deficiency (transferrin saturation less than 20 per cent) was present in the majority of patients in both treatment groups at the start of the study (epoetin β 87 per cent *versus* placebo 80 per cent).

Results

A total of 102 patients could be evaluated in the efficacy analysis.

The median duration of the preoperative epoetin β treatment phase was 5 (range 2–6) days. Median total treatment time was 10 (range 7–15) days. Median cumulative dose in the epoetin β group was 3077 (range 2591–3333) units per kg body-weight.

Table 1 Demographic data and baseline characteristics of the treatment groups at study entry

	Epoetin β (n = 48)	Placebo (n = 54)	P‡
Sex ratio (M:F)	21:27	22:32	n.s.
Age (years)*			
<60	6 (12)	13 (24)	
60–69	12 (25)	19 (35)	
70–79	23 (48)	16 (30)	
≥80	7 (15)	6 (11)	
Median (range) age (years)	71 (53–87)	67 (37–91)	0.047
Blood volume (litres)†	4.4 (3.7–4.9)	4.1 (3.8–5.0)	n.s.
Haemoglobin (g/dl)†	11.5 (10.5–12.5)	12.0 (11.0–12.1)	n.s.
Erythrocyte count (10 ⁶ per μ l)†	4.21 (3.89–4.49)	4.20 (3.90–4.61)	n.s.
Reticulocytes (%)†	1.03 (0.61–1.65)	0.91 (0.43–1.22)	n.s.
Iron (μ mol/l)†	4.05 (2.86–9.07)	6.80 (4.00–12.20)	0.007
Ferritin (ng/ml)†	25.0 (12.2–93.2)	48.0 (17.0–85.6)	n.s.
Transferrin saturation (%)†	6.2 (3.3–13.9)	9.9 (6.6–17.3)	0.015

*Values in parentheses are percentages; †values are median (interquartile range). ‡Fisher's exact test

Total blood loss in the epoetin β group (median 440 (range 150–1970) ml) was slightly higher than that in the placebo group (median 345 (range 50–4000) ml) (P not significant).

Sixteen patients in the epoetin β group (33 per cent) and 15 in the placebo group (28 per cent) received peri-operative blood transfusions ($P=0.67$) (Table 2). Of patients who received blood transfusions, nine in the epoetin β group and 11 in the placebo group were transfused with 1–2 units of blood. Seven (15 per cent) of 48 patients in the epoetin β group and four (7 per cent) of 54 receiving placebo required more than 2 units of homologous blood during the operative period.

Patients receiving epoetin β reached 95 per cent of the baseline haemoglobin value faster than those receiving placebo (median 9.5 versus 22 days) (Fig. 1), but this was not significant ($P=0.27$). At the time of the last follow-up visit (12 weeks), haemoglobin levels were almost equal in both groups (Table 3). The increase in corrected reticulocyte count between baseline and the last preoperative value was significantly higher in the epoetin β group ($P=0.036$) (Fig. 2). Median corrected reticulocyte count changed from 10.3 to 20.2 per cent in the epoetin β group compared with 9.3 and 11.6 per cent in the placebo group. In parallel, median transferrin saturation decreased from 5.6 to 5.4 per cent in the treated patients compared with an increase from 9.9 to 11.9 per cent in the placebo group (Fig. 3). These data suggest stronger erythropoiesis and iron utilization in the epoetin β group. Forty of the 48 patients in the epoetin β group and 48 of the 54 in the placebo group received iron supplements throughout the study. Despite iron supplementation, 82 per cent of the

epoetin β -treated patients and 77 per cent of those receiving placebo still suffered from iron deficiency at the end of the observation period (Table 3).

Univariate logistic regression analysis revealed that higher blood loss, greater age and lower baseline values of haemoglobin and transferrin saturation were the most important predictors for transfusion need ($P<0.05$). Only

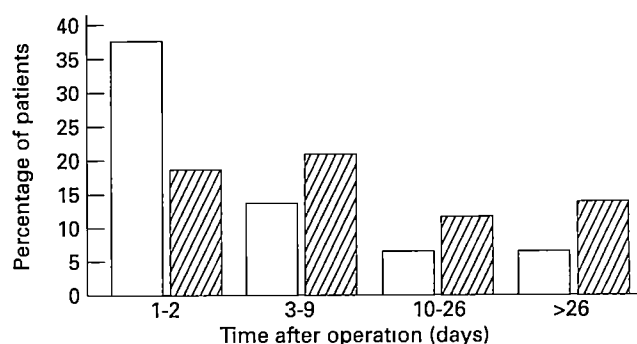


Fig. 1 Proportion of patients reaching 95 per cent of baseline haemoglobin concentration after operation. □, Epoetin; ▨, placebo

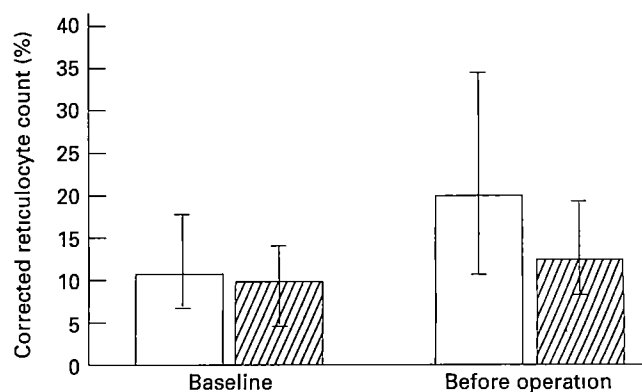


Fig. 2 Change in corrected reticulocyte count between baseline and last preoperative value. Values are median (interquartile range). □, Epoetin; ▨, placebo

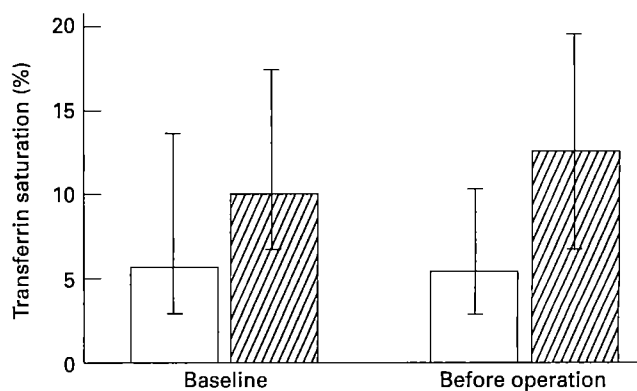


Fig. 3 Change in transferrin saturation between baseline and last preoperative value. Values are median (interquartile range). □, Epoetin; ▨, placebo

Table 2 Amount of blood (erythrocyte concentrate) transfused

	Epoetin β (<i>n</i> = 48)	Placebo (<i>n</i> = 54)
Erythrocyte concentrate (ml per patient)		
0	32 (67)	39 (72)
200–400	1 (2)	3 (6)
401–800	8 (17)	8 (15)
801–1200	3 (6)	3 (6)
1201–1600	1 (2)	0 (0)
>1600	3 (6)	1 (2)

Values in parentheses are percentages

Table 3 Course of haemoglobin and serum iron levels during the study

	Epoetin β (<i>n</i> = 48)	Placebo (<i>n</i> = 54)
Haemoglobin (g/dl)		
Baseline	11.5 (10.5–12.5)	12.0 (11.0–13.1)
1 day before operation	11.4 (10.3–12.6)	11.9 (10.8–12.9)
1 day after operation	11.2 (9.9–12.2)	10.5 (9.6–11.5)
Day 10–12	12.0 (10.7–13.5)	11.3 (10.2–12.2)
Follow-up	13.2 (11.5–13.9)	13.0 (12.5–13.8)
Iron (μ mol/l)		
Baseline	4.05 (2.86–9.07)	6.80 (4.00–12.20)
1 day before operation	3.58 (2.50–6.26)	8.00 (5.70–12.17)
1 day after operation	2.14 (1.61–3.40)	3.22 (1.97–6.26)
Day 10–12	3.90 (2.86–4.65)	5.19 (3.22–8.05)
Follow-up	8.60 (4.47–15.40)	10.11 (6.08–16.30)

Values are median (interquartile range)

Table 4 Results of stepwise multiple logistic regression analysis on prognostic factors and treatment group with respect to the need for blood transfusion

Covariate	Cut-off level*	Odds ratio†	P
Age	70 years	8.10 (2.48–26.41)	0.0005
Haemoglobin level at baseline	11.5 g/dl	0.19 (0.06–0.61)	0.005
Blood loss	500 ml	13.17 (3.72–46.64)	0.0001
Treatment group	Epoetin β versus placebo	0.67 (0.22–2.02)	0.478

Values in parentheses are 95 per cent confidence intervals. *For quantitative variables two subgroups were generated: '<' and '>cut-off'. †If the odds ratio is greater than 1, the risk of blood transfusion is higher in the subgroup above the cut-off level than in that up to the cut-off level

one patient under 70 years of age, with a haemoglobin level above 11.5 g/dl and blood loss of less than 500 ml required blood transfusion, compared with four patients of that age and haemoglobin level with blood loss greater than 500 ml. In contrast, 16 of 24 anaemic patients (haemoglobin level less than 11.5 g/dl) older than 70 years required transfusion, especially if blood loss exceeded 500 ml (eight of nine patients). Calculated blood volume and sex were not predictive. In the multiple logistic regression analysis only blood loss, age and baseline haemoglobin value remained as independent significant predictors (Table 4). The slight tendency for a higher transfusion frequency in the epoetin β group compared with that in the placebo group (odds ratio 1.30) in the analysis without adjustment for the significant predictors was reversed in the adjusted analysis (odds ratio 0.67), without being significant (Table 4).

All 109 patients originally entered into the study were analysed for safety of the applied medication. The demographic data of these patients did not differ in any important respect from those in the 102 patients analysed for efficacy. Twenty (38 per cent) of 52 patients in the epoetin β group and 15 (26 per cent) of 57 who received placebo suffered from adverse events. The majority of adverse effects occurred after operation and during the post-treatment observation period. Four patients were withdrawn from the study owing to adverse events. In two of these patients the adverse effects (chills with fever and constipation) were not serious and occurred during treatment with erythropoietin. Only the event 'chills with fever' was classified as possibly related to epoetin β therapy. The two other patients were withdrawn for serious adverse events during the post-treatment period: one patient (epoetin β) suffered from arterial thrombosis which was resolved by thrombectomy, and the other (placebo) experienced mycotic sepsis. In nine patients from the epoetin β group and in eight from the placebo group, serious adverse events occurred. Six (epoetin β) and four (placebo) of these were disorders of the cardiovascular system. A total of seven patients suffering from serious adverse events died (epoetin β five, placebo two). The causes of death were heart failure due to underlying malignant disease (epoetin β two, placebo two), heart failure due to septicaemia (epoetin β one), cachexia (epoetin β one) and sudden cardiac death of unknown origin (epoetin β one). Five of these patients (epoetin β three, placebo two) died during the post-treatment period. Two patients (epoetin β) died after withdrawal from the

study. All the deaths were classified as unrelated to epoetin β therapy.

Discussion

In view of the risk of transmission of infection, especially hepatitis and human immunodeficiency virus, allogeneic blood transfusions have become more and more restricted over the past 10 years. On the other hand, in 1982 Burrows and Tartter⁴ reported a strong negative influence of perioperative blood transfusion on the prognosis of patients with colorectal cancer. This was followed by a number of reports from groups with similar results, but other authors have questioned blood transfusion as an independent negative prognostic factor^{1,3,5,6,15}.

For colorectal cancer the percentage of patients receiving perioperative blood transfusions is between 45 and 86 per cent^{1–3}. Patients with cancer of the right hemicolon can be expected to be anaemic more frequently than those with tumours at other locations, and in consequence they are more likely to be transfused. Surprisingly, the overall transfusion frequency in this study of right hemicolectomy was only 30 per cent. One reason for this obvious difference is that the indication for transfusion was set at a haemoglobin concentration of 7.5 g/dl or lower, which is a value well tolerated by most patients. Experimental data¹⁶ also support the use of this low haemoglobin level. In addition the low rate of transfusion reflects the generally changed attitude towards blood transfusion based on the experience of recent years.

Recombinant human erythropoietin is currently used widely to correct the chronic anaemia of end-stage renal disease. It has been demonstrated that lack of endogenous epoetin β production is the main cause of anaemia in these patients¹⁷. In anaemic patients with cancer, the serum levels of erythropoietin are below those of patients with iron deficiency anaemia^{18,19}. This blunted epoetin β response to chronic anaemia can be corrected by subcutaneous injection of epoetin β 22–300 units per kg body-weight three times per week^{20,21}, with an increase in haemoglobin levels within several weeks. Based on this, erythropoietin can also be used to prevent chemotherapy-induced anaemia¹².

In healthy subjects undergoing elective hip surgery, extensive programmes for predeposit autologous blood donation have been initiated. Epoetin β was used in these patients at a dose of 600 units/kg two times weekly for 3 weeks. The amount of collected blood and, in consequence, the need for allogeneic blood transfusion can be reduced with recombinant erythropoietin^{10,22}.

In the present study, a high dose of erythropoietin (20 000 units/day) was chosen in view of the short treatment interval of 5–10 days before operation, and a total maximum treatment time of 10 days. The main indicators for blood transfusion requirement in this study were patient age over 70 years, baseline haemoglobin concentration below 11.5 g/dl and cumulative blood loss greater than 500 ml. With the chosen erythropoietin regimen, it was not possible to reduce the need for perioperative blood transfusion significantly. None the less, epoetin β was effective in stimulating erythropoiesis at the time of operation, as indicated by the large pre-operative increase in reticulocyte count. In parallel, transferrin saturation and the iron levels of the epoetin β -treated patients suggest a more pronounced stimulation than in control patients.

In a similar study using a lower dose of epoetin β , 150 units/kg every 2 days for 10 days before surgery²³, it was also not possible to reduce the transfusion requirement. In contrast, in a study with a small number of slightly anaemic patients with gastric and colorectal cancer, treatment with epoetin β facilitated preoperative blood donation and reduced the need for homologous blood transfusion²⁴. In this study, epoetin β was given at a dose of 300 units/kg followed by 100 units/kg on days 4, 8 and 12.

Treatment with subcutaneous erythropoietin at the dose chosen in this study was well tolerated by patients. Serious adverse events related to erythropoietin were not observed. One patient experienced arterial thrombosis 7 days after completion of epoetin β therapy; thrombocyte counts were within the normal range, and thrombectomy was performed successfully. This adverse event was classified as unrelated to epoetin β treatment.

In conclusion, it can be stated that the amount of blood transfused over the operative period cannot be reduced by the short-term application of erythropoietin 20000 units per day in anaemic patients with colorectal cancer undergoing right hemicolectomy. This is probably a result of the inadequate preoperative treatment period of only 5 days. The generally low transfusion frequency in this study and the iron deficiency in almost all patients possibly contributed to this negative result. The administration of erythropoietin to patients with colonic cancer is well tolerated and safe. Future studies may be attempted with a longer duration of treatment. This might become possible if therapy could be started immediately after confirming diagnosis in the outpatient setting.

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Matrix metalloproteinase 9 level predicts optimal collagen deposition during early wound repair in humans

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Background This study examined two matrix metalloproteinases (MMPs) and their association with deposition of collagen during wound repair.

Methods In 15 hernia wounds, wound fluid was collected using two Cellstick devices, which were implanted adjacent to two expanded polytetrafluoroethylene (ePTFE) tubes. MMP-2 and MMP-9 levels were analysed 24 and 48 h after operation using specific enzyme-linked immunosorbent assays, and collagen deposition in the ePTFE tubes was measured 10 days after operation as hydroxyproline.

Results The levels of both MMPs in wound fluid were increased compared with those of control serum, although MMP-9 decreased ($P < 0.01$) in the wounds 24–48 h after operation. The MMP-9 level at 24 h correlated inversely and specifically to deposited collagen measured as hydroxyproline ($r_s = -0.80$, $P < 0.01$).

Conclusion These results indicate that the level of MMP-9 in the early inflammatory phase can predict the amount of collagen deposited later in the wound healing process.

Reliable biochemical markers of wound repair are required to predict the outcome of wound healing. The authors have previously examined the use of the Cellstick device (Cellmeda, Turku, Finland) in different experimental and clinical situations^{1,2}. Wound fluid and inflammatory cellular infiltrate can be collected relatively non-invasively with the Cellstick device during the first 72 h after operation. A correlation was demonstrated between cytological findings and the tensile strength that developed later in incisional wounds made in the skin of guinea-pigs². However, because of the variability of cytological examination, a more precise marker is needed. Furthermore, tensile strength measurements cannot be carried out in humans for ethical reasons.

Collagen (measured as hydroxyproline) deposition, as a biochemical marker of wound healing, has been studied under standardized conditions in humans by implanting expanded polytetrafluoroethylene (ePTFE) tubes subcutaneously³. The ePTFE model has been used successfully to document the influence of systemic and local factors on the wound repair response and was found in one study to induce more collagen than polyvinyl alcohol sponges^{3–5}.

The amount of collagen laid down in wounds is the net result of collagen synthesis and degradation. Degradation is accomplished by a family of proteolytic enzymes called matrix metalloproteinases (MMPs) with at least 11 members, the collagenases, stromelysins, gelatinases and matrilysin^{6,7}. MMPs have different substrate specificity for extracellular matrix constituents and have a major role in wound healing^{8–11}. MMPs are secreted in latent (inactive) forms, which are incapable of proteolysis. Latency is maintained by the linkage between cysteine in the pro-enzyme domain and zinc at the catalytic site. The activation processes in tissue are unclear but *in vitro* the organomercurial aminophenylmercuric acetate and the

detergent sodium dodecyl sulphate can activate the enzymes^{6,12}. Once activated, another line of control of degradation is exerted by tissue inhibitors of metalloproteinases, which bind to the active enzymes with high affinity⁶. Because knowledge of the quantitative correlation between MMPs and collagen deposition during wound repair is lacking⁸, this study was carried out to examine the predictive value of two MMPs, MMP-2 (also called gelatinase A) and MMP-9 (gelatinase B) on collagen deposition. For this purpose the two devices, Cellstick and ePTFE, were implanted adjacent to one another in hernia wounds to monitor postoperative wound healing.

Patients and methods

Patients and surgery

Patients for elective primary groin hernia repair under general anaesthesia were asked to participate in a wound healing study, approved by the local ethics committee (Copenhagen V01-507/93). Before inclusion the patients were fully informed about the procedures, and the implant devices used for the study were shown to them. Written informed consent was obtained from the patients.

Fifteen patients (13 men) of median age 65 (interquartile range (i.q.r.) 37–77) years participated in the study. Two Cellstick devices (a high-grade viscose cellulose sponge (length 2 cm, width 0.13 cm) within a special wound drain of a thin silicone rubber tube (length 15 cm, inner diameter 0.18 cm, outer diameter 0.25 cm)¹ and two ePTFE tubes (length 6 cm, inner diameter 0.12 cm, outer diameter 0.24 cm, pore size 90–120 µm, OEM-012-01; International Polymer Engineering, Tempe, Arizona, USA)³ were implanted into the subcutaneous wound cavity close to the muscular fascia. The wound was closed by a running monofilament 3–0 polyamide suture. The incision was covered with a hydrocolloid dressing and the ends of the Cellstick tubes were covered with an absorbent dressing, allowing free flow of wound fluid.

A control group consisting of five healthy volunteers (four men and one woman of median age 46 (i.q.r. 41–48) years) was included to provide serum.

Postoperative handling of wound healing devices

One Cellstick was withdrawn 24 h and the other 48 h after operation. The accumulated wound fluid (about 0.3 ml) was obtained with 1 ml RPMI-1640 (Sigma, St Louis, Missouri, USA) using a turbulent, pulsating, retrograde washout process including an automatic pump, according to the manufacturer's instructions, cleared by centrifugation (1500 r.p.m.) and stored at -70°C until analysed for MMPs and protein. Recovery experiments demonstrated no significant binding of MMPs to the cellulose viscose sponge or to the silicone rubber. The two ePTFE tubes were withdrawn on the tenth postoperative day, placed into acetone and stored at 4°C until analysis for hydroxyproline and proline.

Biochemical analysis

MMP-2 and MMP-9 levels were measured with specific enzyme-linked immunosorbent assays (ELISAs)^{13,14}. The MMP-2 kit was purchased from Fuji Chemical Industries (Takaoka, Japan) and the reagents for MMP-9 determination were generously provided by Dr L. Kjeldsen, Department of Haematology, Rigshospitalet, Copenhagen, Denmark. The MMP levels were normalized to the amount of protein determined using the Bradford dye-binding procedure with bovine serum albumin as standard (Bio-Rad; Hercules, California, USA).

Hydroxyproline and proline were measured colorimetrically in three separate 1-cm segments of each ePTFE tube hydrolysed in hydrochloric acid 6 mol/l¹⁵.

Wound fluids, and extracts of skin and wound tissue, were also subjected to zymographic analysis as described elsewhere⁹. In addition gelatinolytic activity was determined in representative wound fluids using the gelatin substrate followed by separation of digestion products by sodium dodecyl sulphate polyacrylamide gel electrophoresis¹⁶.

Statistical analysis

Results are expressed as median (i.q.r.) and analysed with Statgraphics Plus 5.2 software (Statistical Graphics Corporation, Rockville, Maryland, USA). Comparisons between groups were carried out using the Wilcoxon signed rank test. The relationship between MMP and hydroxyproline and proline levels respectively was evaluated by Spearman's rank correlation test. $P < 0.05$ was considered statistically significant.

Results

A continuous flow of wound fluid from the wound cavity via the Cellstick device into the absorbent dressing was observed in all patients. The implantation and presence of wound healing devices did not cause any wound complications, nor did any wound infection develop subsequently.

Because the antibodies used in the ELISAs show diminished immunoreactivity to the active gelatinase species, there was concern about detecting all the enzymes. However, it was seen from the zymogram that no, or undetectable, levels of active MMP-2 or MMP-9 were present in the wound fluid samples, although active MMP-9 species were seen in crude extracts of wound tissue (Fig. 1). These results were confirmed using an alternative gelatinase activity assay; wound fluid without activation showed no gelatinolytic activity whereas activation of the same wound fluid samples was associated with complete degradation of gelatin after 24 h (Fig. 2).

Immunoreactive MMP-2 and MMP-9 levels in serum from healthy volunteers were 8.0 (6.9–9.0) and 3.2 (2.4–5.2) ng per mg protein respectively. Temporal changes in wound fluid for the two MMPs revealed that MMP-2 concentration increased from 24 h (14.6 (8.6–18.0) ng per mg protein) to 48 h (16.2 (11.1–18.1) ng

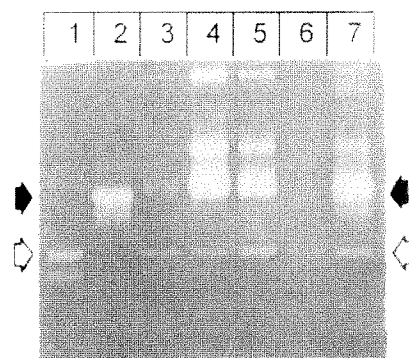


Fig. 1 Zymogram of wound fluid, and extracts (in 20 volumes of 0.25 per cent (v/v) Triton X-100, calcium chloride 0.01 mol/l) of normal human skin and day 10 wound tissue (expanded polytetrafluoroethylene (ePTFE) tube). The gelatin substrate (0.2 mg/ml) was incorporated in the 7.5 per cent sodium dodecyl sulphate polyacrylamide gel and samples were electrophoresed at 100 V for 2 h⁹. The gel was then incubated in a buffer (calcium chloride 0.01 mol/l, 1 per cent (v/v) Triton X-100, 0.02 per cent sodium azide, zinc chloride 1 $\mu\text{mol/l}$, Tris-hydrochloric acid 0.05 mol/l, pH 7.5) for 18 h at room temperature, washed in deionized water, stained in colloidal Coomassie Blue G-250 and destained in deionized water. The lanes represent from left to right: 1, matrix metalloproteinase (MMP) 2 standard (0.5 ng); 2, MMP-9 standard (0.1 ng); 3, serum (2 μg); 4, wound fluid at 24 h (2 μg); 5, wound fluid at 48 h (2 μg); 6, skin extract (1 μl); 7, ePTFE tube extract (1 μl). Open arrows represent the position of proMMP-2 and closed arrows proMMP-9. The two bands above MMP-9 at about 125 and 215 kDa in lanes 3, 4, 5 and 7 probably represent microglobulin bound to a monomer and dimer of MMP-9 respectively. Addition of the chelator 1,10-phenanthroline (2 mmol/l) to the incubation buffer abolished all enzymatic activity

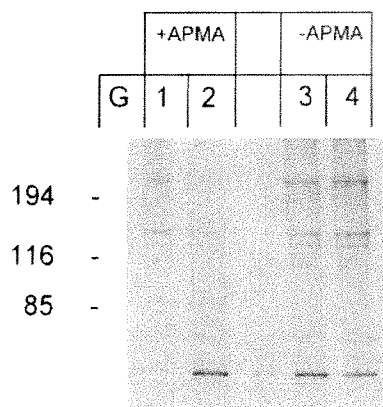


Fig. 2 Gelatinolytic activity of 24-h wound fluid with (lanes 1 and 2) and without (lanes 3 and 4) the presence of aminophenylmercuric acetate (APMA) 0.5 mmol/l. Wound fluid was incubated with the gelatin substrate (G; 10 μg) for 4 h (lanes 1 and 3) and 24 h (lanes 2 and 4) at 37°C in assay buffer (sodium chloride 0.2 mol/l, calcium chloride 0.01 mol/l, 0.03 per cent (v/v) Brij-35, 0.02 per cent sodium azide, Tris-hydrochloric acid 0.05 mol/l, pH 7.5). The degradation products were separated on 7.5 per cent sodium dodecyl sulphate polyacrylamide gel electrophoresis, the gel was stained in colloidal Coomassie Blue G-250 and destained in deionized water. High molecular weight standards (Bio-Rad) were run simultaneously and the positions are indicated on the left in kilodaltons

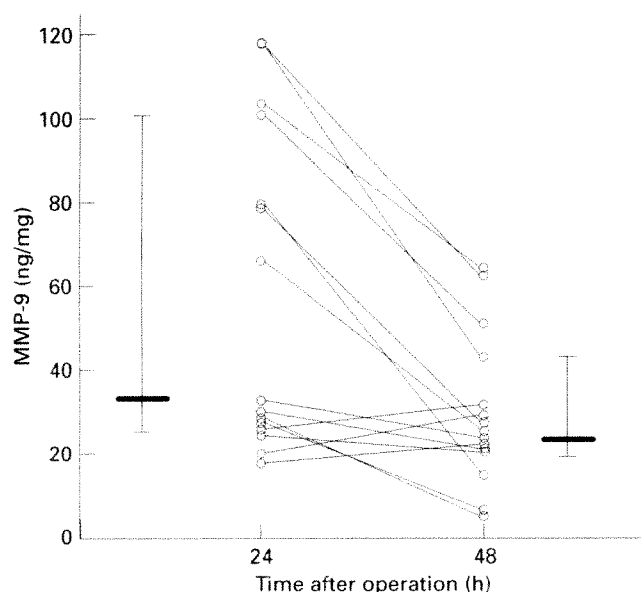


Fig. 3 Matrix metalloproteinase (MMP) 9 level 24 and 48 h after operation in wound fluid obtained using Cellstick in 15 patients. Median values and interquartile ranges at 24 and 48 h are also shown. The level of MMP-9 at 48 h was significantly lower than that at 24 h ($P < 0.01$, Wilcoxon signed rank test)

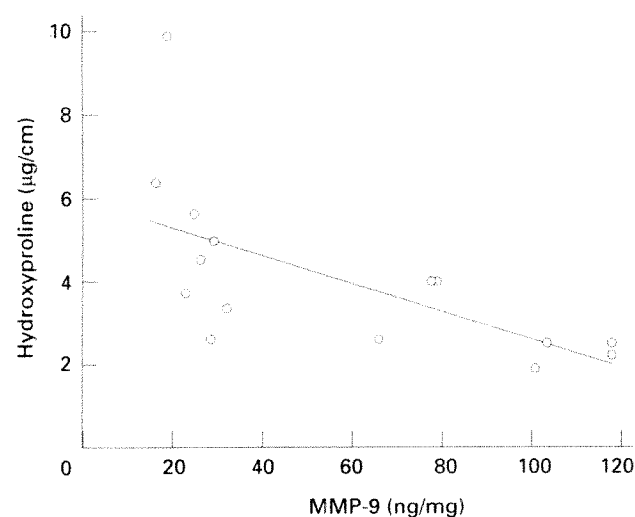


Fig. 4 Relationship between deposited collagen on postoperative day 10 (measured as micrograms of hydroxyproline per centimetre length of expanded polytetrafluoroethylene tube) and matrix metalloproteinase (MMP) 9 concentration in wound fluid at 24 h in each of the 15 patients ($r_s = -0.80$, $P < 0.01$)

per mg protein) postimplantation, although this change was not statistically significant ($P = 0.12$, Wilcoxon signed rank test), whereas the level of MMP-9 decreased significantly ($P < 0.01$, Wilcoxon signed rank test) from $33.0(25.8-100.9)$ ng per mg protein at 24 h to $24.4(19.0-43.2)$ ng per mg protein at 48 h (Fig. 3). Essentially identical results were found when zymographic analysis was applied, i.e. MMP-2 lysis bands at 48 h were increased compared with those at 24 h and lysis bands at the

position of MMP-9 at 48 h were decreased compared with those at 24 h (Fig. 1). Furthermore, a similar pattern of gelatinolytic species was seen in extracts of 10-day-old wound tissue in relation to that of wound fluids (Fig. 1). Gelatinolytic activity in wound extracts was also increased compared with that in uninjured skin, which lacked detectable MMP-9 activity (Fig. 1).

Spearman's rank correlation test was used to test the association between MMP levels and deposited hydroxyproline (as a measure of collagen). MMP-9 concentration at 24 h was correlated with decreased collagen content at 10 days ($r_s = -0.80$, $P < 0.01$) (Fig. 4). There was no statistically significant correlation ($r_s = 0.33$, $P = 0.22$) between MMP-9 concentration at 24 h and proline levels on day 10.

Discussion

Extracellular matrix molecules are crucial in tissue repair and ideally there should be a balance between the anabolic and catabolic processes regulating them. MMPs participate in the degradation of the extracellular matrix molecules, native and denatured collagens, elastin, laminin and fibronectin, although the roles of the individual MMPs are largely unknown. These findings, using standardized and validated models in human wounds and specific ELISAs, indicate that wounding induces both MMP-2 and MMP-9, but to varying degrees. MMP-2 concentration was increased about twofold and that of MMP-9 about tenfold compared with levels in serum, which represents an uninjured state. Furthermore, raised levels of MMP-9 during the early inflammatory phase are specifically associated with a decreased amount of collagenous proteins.

Because MMP-9 concentration decreased after operation, an increased MMP-9 level may indicate a delayed wound healing response resulting in less collagen deposition. This hypothesis is supported by studies on non-healing chronic wounds and on surgical wounds with complications^{11,17}. In both these clinical situations, characterized by impaired healing, persistently raised MMP-9 levels, measured by substrate gel electrophoresis, were found.

Interestingly, levels of the fibroblast-derived MMP-2 appeared to increase as early as 24 h after operation, compared with levels in serum. This finding indicates an early activation of fibroblasts in the wound healing process. However, the temporal changes of MMP-2 were much less pronounced than those of MMP-9, as has been reported earlier in wounds of the skin and the oral cavity⁹⁻¹¹. Beyond 48 h after operation MMP-2 concentration appears to be stably increased for a prolonged period of time⁹. This finding indicates a less prominent role of MMP-2 in early granulation tissue metabolism but possibly an involvement in later remodelling stages of wound repair.

Only latent MMP enzymes could be detected in the wound fluid, as seen by both the zymographic and gelatinase assays. However, it is possible that active enzymes are retained in the tissue and thus not detected in wound fluid owing to high affinity of active enzymes for collagenous molecules¹⁸. Another explanation may be that MMP-9 is secondary to some other mechanism(s) regulating collagen deposition. Previously, the authors have demonstrated the predictive power of early inflammatory events on wound healing². Because MMP-9 is made by

polymorphonuclear leucocytes and monocytes-macrophages, it is possible that MMP-9 is a marker of the activities of these cells rather than participating directly in collagen metabolism in the wound tissue. The regulation of MMPs is largely unknown. For example, interleukin 6 levels did not change from 24 to 48 h after operation in the fluids from these wounds (data not shown).

Although wound healing was not measured *per se* but indirectly as hydroxyproline concentration, Wicke *et al.*¹⁹ have documented a correlation between deposition of collagen in ePTFE tubes and the tensile strength of incisions in the skin of rats. Furthermore, Oxlund *et al.*²⁰ recently showed a parallelism between skin wounds and colon anastomosis regarding collagen synthesis and wound strength in the rat. Therefore, it is possible that the subcutaneous monitoring system can also predict general healing potential such as anastomotic healing in the intestine.

Whatever the function of MMP-9, it appears to be an early and reliable marker of collagen deposition during wound repair.

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Effect of colonic obstruction on the distribution of matrix metalloproteinases during anastomotic healing

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Background Anastomotic dehiscence is common after surgery for colonic obstruction. The strength of an anastomosis is dependent on collagen, which is degraded by matrix metalloproteinases (MMPs).

The aim of this study was to determine the distribution of the MMPs and their inhibitor, tissue inhibitor of metalloproteinases (TIMP) 1 in an experimental model of colonic obstruction, with and without resection and anastomosis.

Methods The distal colon of rabbits was obstructed with a Silastic ring for 24 h and then either the ring was removed or the obstructed segment was resected and an anastomosis formed. Rabbits were killed immediately or at intervals for up to 7 days after operation. The distribution of the MMPs and TIMP-1 was examined by indirect immunofluorescence.

Results MMPs and TIMP-1 were present throughout the descending colon for 24 h in both groups. They persisted to the third day in rabbits with an anastomosis but by day 7 were restricted to the suture line. Their presence correlated with microscopic damage.

Conclusion The extensive distribution of the MMPs suggests that these enzymes contribute to anastomotic dehiscence, but only in the immediate postoperative period.

Several factors have been recognized that influence colonic healing unfavourably, including primary anastomosis after resection for colonic obstruction. Irvin and Goligher¹ reported a clinical leak rate of 24 per cent when obstruction was present, compared with 14 per cent following resection of non-obstructed colon. Although improvements in operative technique have reduced the incidence of anastomotic dehiscence after surgery for an obstructed colon to 7 per cent^{2–4}, morbidity remains high⁵.

The collagen content of the submucosa determines the strength of the colon, and its integrity is important for healing⁵. Hawley and colleagues⁶ demonstrated that the colon has a higher collagenolytic activity than other regions of the gastrointestinal tract. Several groups^{7–9} subsequently reported a decrease in collagen concentration at the anastomotic site, associated with a decrease in bursting pressure¹⁰. Anastomotic dehiscence has therefore been attributed to excessive collagenase activity.

Collagen and other extracellular matrix components are degraded by a family of enzymes, the matrix metalloproteinases (MMPs), which between them digest all the components of the matrix¹¹. The enzymes examined in this study, with the exception of polymorphonuclear leucocyte gelatinase, are produced on demand and secreted in precursor form. The presence of intracellular enzyme shows that synthesis has been activated but the enzymes function only at the extracellular level. Active MMPs are inhibited by a specific group of inhibitors, tissue inhibitors of metalloproteinases (TIMPs).

Previous studies^{12–14} of MMPs after colonic resection and anastomosis have shown that they are restricted to the suture line and that TIMP-1 is present at the same

site. If the colon was ischaemic before resection and anastomosis, MMPs were observed several centimetres from the suture line^{13,14}. Obstruction alters colonic collagen content and synthesis at and beyond the suture line¹⁵. Therefore, to determine whether the breakdown of collagen is also influenced by obstruction, MMPs were investigated by indirect immunofluorescence in the colon of rabbits either following obstruction alone or after resection of the obstructed site with anastomosis.

The anastomosis was studied after 12 and 24 h to examine the early events during the acute phase, when bursting pressure is at its lowest¹⁶, and after 3 days, which is the phase when the inflammatory infiltrate becomes dominated by macrophages and lymphocytes¹⁶ and anastomotic collagen levels are at their lowest¹⁵. The final investigation was after 7 days when the collagen level has returned at least to normal¹⁰ and a fibrous scar has formed which will undergo remodelling^{12,13}.

Materials and methods

All operative procedures were carried out under anaesthesia induced with Hypnorm (fentanyl citrate fluanisone; Janssen Pharmaceuticals, Grove, UK) 0.3 ml/kg and diazepam (Phoenix Pharmaceuticals, Gloucester, UK) 2 mg/kg, and maintained as required with Hypnorm.

Distal colonic obstruction was produced experimentally for 24 h in female New Zealand White rabbits (2–2.5 kg) using a Silastic (Dow Corning, Reading, UK) ring 5 mm in width of internal diameter half that of normal colon. Preliminary experiments had demonstrated that this resulted in a partially obstructed colon without necrosis^{12–14}. To eliminate artefactual changes caused by the Silastic material, a ring of the same diameter as the colon was also placed around and in contact with the bowel wall for 24 h. The rabbits were killed and the bowel was resected for examination.

After 24 h either the ring was removed or the obstructed (ring) site was resected and an anastomosis was carried out with a single layer of interrupted extramucosal 6/0 silk sutures

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(Ethicon, Edinburgh, UK). On average 12 sutures were inserted. The abdomen was closed in two layers with continuous 2/0 polyglycolic acid sutures (Dexon; Cyanamid, Gosport, UK).

Three rabbits in both groups were killed immediately (0 h) after removal of the ring or formation of the anastomosis, three after 24 h and three after 3 days. Three rabbits with resection and anastomosis were also killed 12 h and 7 days after operation.

Tissue was sampled in 2-cm segments from the sites shown in Fig. 1a. Initial measurements indicated more extensive changes than expected; therefore, for the studies on obstruction with release of the ring, 2-cm segments of tissue were also taken from the transverse and ascending colon (Fig. 1b).

The segments were divided into two; one was placed in formalin for routine processing, wax embedding and staining (5- μ m sections with haematoxylin and eosin stain) and the other was placed in 7 per cent gelatin and snap-frozen in liquid nitrogen for MMP immunolocalization.

An indirect immunofluorescence technique was employed for identification of MMPs and TIMP-1 using the antisera (provided by Strangeways Research Laboratory, Cambridge, UK) and methodology described previously¹²⁻¹⁴. Sections were viewed by fluorescence microscopy using epifluorescence and standard wide-band fluorescein isothiocyanate (FITC) filters (Leitz, Milton Keynes, UK).

Results

After 24 h of obstruction the colon proximal to the ring was seen to be distended approximately to twice normal size for about 30 cm, that is to the junction of the transverse and descending colon (segment Prox2; Fig. 1b). Distal to the ring the bowel was collapsed. The distension persisted for 24 h after removal of the ring or after resection and anastomosis, but by the third day the colon had returned to normal.

Tissue removed from the ring site and proximal and distal to it in control rabbits (non-constricting ring) was

histologically normal. MMPs and TIMP-1 were not present.

Rabbits with obstruction only

In the first 24 h after release of the ring, the histological changes seen at the ring site and proximally for 25 cm were patchy loss of the epithelial border with some destruction of crypts. In all layers of the colonic wall an acute inflammatory cell infiltrate, oedema, especially of the submucosa, and haemorrhage were observed (Fig. 2). The abnormalities were most severe in the two immediately proximal segments; they were only slight in the ring, distal and Prox2 segments, whereas the transverse and ascending colon always had a normal histological appearance. By the third day the only abnormalities remaining were the occasional loss of the epithelial border and slight oedema of the submucosa.

At the ring site only gelatinase B was present within polymorphonuclear leucocytes. This, too, was the dominant component of the MMPs proximal to the ring site, persisting for 3 days, but cells were fewer and confined to the segments nearest the ring site with time (Table 1). Collagenase, stromelysin, gelatinase A and TIMP-1 were observed within fibroblast-like cells although less frequently than gelatinase B, and similarly the cells became fewer in number with distance from the ring site and with time after release of the obstruction. Extracellular collagenase, stromelysin, gelatinase A and TIMP-1 were seen only immediately after releasing the ring and were restricted to the mucosa of segments immediately proximal and distal to the ring (Table 1).

Tissue from rabbits with resection and anastomosis

From immediately after the formation of an anastomosis and continuing for 3 days thereafter, histologically there was a loss of the epithelial border, submucosal oedema and inflammatory cell infiltrate throughout the colonic wall in all the segments of the descending colon examined. Histological changes were similar to those with oedema only; however, there was greater crypt destruction and the abnormalities persisted for longer (Fig. 3). At the suture line a fibrin clot filled the gap between the cut ends of the bowel from 12 h after anastomosis. By 7 days this had developed into a mature fibrous scar, with restoration of the epithelial border.

MMPs were evident in all the segments examined for the first 24 h after anastomosis, with staining becoming less intense and more patchy the further the distance from the anastomotic segment (Table 2). They were observed extracellularly on the mucosal stroma, with collagenase distributed most extensively, although stromelysin and gelatinase A were also present. In the submucosa, only collagenase was present extracellularly. Throughout the segments investigated, gelatinase B within polymorphonuclear leucocytes was the dominant feature. The other enzymes were present in a few fibroblast-like cells. Extracellular and intracellular TIMP-1 was seen at the same sites as the MMPs but did not stain as intensely and was not present in all sections. On the third day after anastomosis the only difference in the distribution of MMPs was that stromelysin was the most widespread extracellular enzyme. By the seventh day, MMPs and TIMP-1 were restricted to the anastomotic segment (Table 2). In the mucosa, only stromelysin was present. Collagenase was the most widespread extracellular

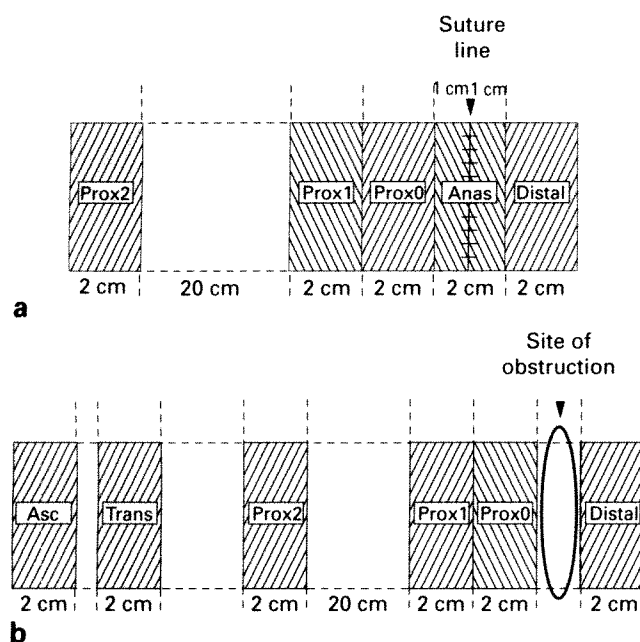


Fig. 1 Diagram showing the segments of colon removed for histological examination and staining for matrix metalloproteinases following a resection and anastomosis and b obstruction followed by removal of the ring. Anas, anastomosis; Asc, ascending colon; Prox, proximal colon; Trans, transverse colon

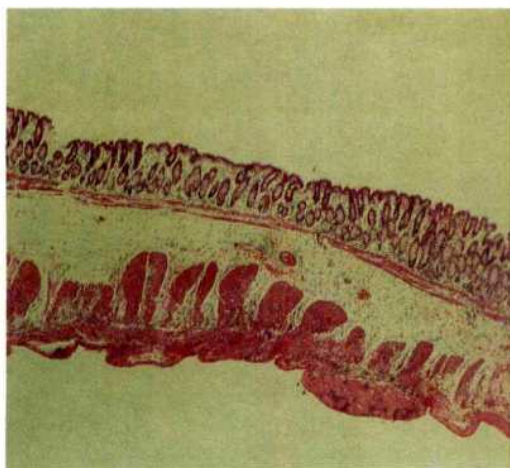


Fig. 2 Section of colon taken from the ring segment following 24 h of obstruction and stained with haematoxylin and eosin. Oedema is present in all layers, but is most extensive in the submucosa. Some patchy loss of the epithelial border and haemorrhage in all layers can also be observed. (Original magnification $\times 40$)



Fig. 3 Section of colon taken from immediately proximal to the ring segment on the third day after resection and anastomosis, and stained with haematoxylin and eosin. Following obstruction, then resection and anastomosis, there is destruction of the mucosal crypts and extensive oedema and inflammatory cell infiltration in all layers. (Original magnification $\times 40$)

Table 1 Distribution of matrix metalloproteinases in the colon of rabbits after 24 h of obstruction then release of the ring

	Collagenase	Stromelysin	Gelatinase A and B	TIMP-1
Mucosa				
0 h	++	++	+++	++
Day 1	++	+	+++	+
Day 3			+	
Submucosa				
0 h	+++	+++	+++	++
Day 1	+++	+++	+++	++
Day 3		+	++	+
Muscle				
0 h	++	++	+++	++
Day 1	++	++	++	++
Day 3	+		+	

TIMP-1, tissue inhibitor of metalloproteinases 1. +, Matrix metalloproteinases (MMPs) or TIMP-1 seen in only a few of the segments examined; ++, MMPs or TIMP-1 observed in most of the segments investigated; +++, MMPs or TIMP-1 seen in all segments examined

enzyme in the fibrous scar, although stromelysin and gelatinase A were also present; TIMP-1 was also found.

Discussion

Experimental colonic obstruction causes the MMPs to be observed not only at the site of obstruction but throughout the proximal colon. They are absent in normal colon as demonstrated in the control rabbits used in this study, confirming previous observations¹²⁻¹⁴.

In this study, the distribution of MMPs corresponded with the microscopic changes caused by obstruction. Histologically, there was some loss of the epithelial border and crypts, and oedema of the submucosa in the obstructed bowel, which resolved rapidly after removal of the constricting ring. By the third day, normality was almost restored. Return to normal requires the break-

Table 2 Distribution of matrix metalloproteinases in the colon of rabbits after 24 h of obstruction followed by resection and anastomosis

	Collagenase	Stromelysin	Gelatinase A and B	TIMP-1
Mucosa				
0 h	+++	++	++	++
12 h	+++	+++	+++	++
Day 1	+++	+++	+++	++
Day 3	+	+++	+++	++
Day 7		+		
Submucosa				
0 h	+	+	++	+
12 h	+	+	+++	+
Day 1	++		+++	+
Day 3	+	+	+++	+
Day 7	+	+	+	+
Muscle				
0 h			++	
12 h			+++	
Day 1			+++	
Day 3			+++	
Day 7			+	

TIMP-1, tissue inhibitor of metalloproteinases 1. +, Matrix metalloproteinases (MMPs) or TIMP-1 seen in only a few of the segments examined; ++, MMPs or TIMP-1 observed in most of the segments investigated; +++, MMPs or TIMP-1 seen in all segments examined

down of damaged extracellular material and synthesis of new. On the mucosal stroma the MMPs, predominantly collagenase, were present extracellularly. Only active collagenase can bind to collagen¹⁷; therefore, degradation of the matrix was taking place at this time. Oedema in the submucosa probably results in distortion of the collagen fibres, and gelatinase degrades denatured collagen. The low level of gelatinase suggested by the presence of intracellular enzyme is probably sufficient for the remodelling required. Although no extracellular enzyme

was observed in the submucosa, when more sensitive techniques such as confocal microscopy are used, intracellular enzyme is seen always to be accompanied by extracellular enzyme (unpublished observations). The rapid return to normal suggests that, in addition to collagen breakdown, collagen synthesis must also be increased. Tornqvist and colleagues¹⁸ studied rats with an obstructed colon and found that collagen synthesis was increased not only at the site of obstruction, but also in the proximal bowel.

When resection and anastomosis was carried out for obstructed colon, the histological damage and distribution of MMPs were similar to, although more exaggerated than, those following obstruction alone. The changes persisted for 3 days for several centimetres proximal to the suture line. This pattern is in contrast to that following resection and anastomosis alone, where both the histological abnormalities and the MMPs were observed only at the suture line¹²⁻¹⁴. By the seventh day, MMPs and TIMP-1 were localized mainly to the fibrous tissue, identical to findings following anastomosis in an unobstructed colon¹²⁻¹⁴.

Changes in collagen metabolism have been examined in two other studies of obstruction and anastomosis. Jiborn *et al.*⁹ found that partial obstruction caused by continuous suturing resulted in a decrease in collagen concentration compared with an interrupted sutured anastomosis. Tornqvist *et al.*¹⁵ also reported a decrease in collagen concentration, although the collagen content was increased, as was collagen synthesis. Surprisingly, the collagen content was the same in rats with anastomosis only. As synthesis was higher than in this latter group, it is implied that collagen degradation must also be higher in obstructed colon. This is supported in the present study by the more widespread distribution of MMPs in an obstructed colon compared with that in anastomosis alone¹²⁻¹⁴.

The strength of the colon is dependent on the presence of mature collagen, primarily in the submucosa⁵. Therefore, the damage and breakdown of mature collagen with synthesis of new, initially immature, collagen in an obstructed colon could lead to a weaker bowel wall. Hence, MMPs could be a contributory factor in delayed healing of the anastomosis in an obstructed colon.

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Temporary decompression after colorectal surgery: randomized comparison of loop ileostomy and loop colostomy

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Background Loop ileostomy or loop transverse colostomy for temporary decompression of a left colonic anastomosis represents an important issue in abdominal surgery.

Methods A randomized study, comparing loop ileostomy ($n = 37$; group 1) or loop transverse colostomy ($n = 39$; group 2), was conducted. Patients were followed from construction to closure of the stoma.

Results Age, weight, sex and indication for surgery were similar in both groups. After stoma construction complications were reported in nine of 37 patients in group 1 and in one of 39 in group 2 ($P < 0.01$), leading to postoperative death in five of 37 in group 1 and one of 39 in group 2. In the period between stoma construction and closure significant differences were observed only in prolapse rate (one of 32 group 1, 16 of 38 group 2; $P < 0.01$), need for temporary adaptation of clothing (eight of 32 group 1, 22 of 38 group 2; $P < 0.01$) and dietary guidelines (23 of 32 group 1, four of 38 group 2; $P < 0.01$). One patient died in group 1 and four in group 2; the deaths were not stoma related. After stoma closure eight of 29 patients in group 1 had complications and there were two deaths compared with three of 32 and no deaths in group 2.

Conclusion Both types of stoma carry a high complication rate with a considerable associated mortality rate. The interval between stoma construction and closure has substantial impact on social and economic status. Based on all three phases studied, routine use of transverse colostomy is advised if decompression of the left colon is indicated.

Decompression of a left colonic anastomosis by a loop ileostomy or loop transverse colostomy represents an important issue in abdominal surgery. Several studies^{1–7} have addressed the question of which of these stomas should be used when a left colonic anastomosis needs decompression. Two randomized^{1,2} studies and five non-randomized studies^{3–7} have not provided a definitive answer nor have they covered all the relevant aspects of stoma creation, stoma ownership and stoma closure. A prospective defunctioning stoma trial in 76 patients, operated on under acute and elective conditions, is now reported. The morbidity and mortality rates associated with loop ileostomy and loop transverse colostomy at all three stages are reported and discussed.

Patients and methods

Between 1990 and 1995 a randomized multicentre study was conducted in five Dutch surgical centres to compare loop ileostomy with loop transverse colostomy. All patients undergoing colorectal surgery who were likely to need a defunctioning stoma were eligible for inclusion and were asked to give informed consent. The final decision about the need for construction of a defunctioning stoma was made at operation. Construction of a loop ileostomy or loop colostomy and a planned elective stoma closure operation were criteria for inclusion. The patients were randomly allocated to loop ileostomy or loop transverse colostomy.

Seventy-six patients were recruited; 37 patients had a loop ileostomy and 39 a loop transverse colostomy. The two groups were comparable with respect to age, weight, sex and primary

pathology (Table 1). Patients were operated primarily for malignancy of the left-sided colon or rectum, for complicated diverticular disease, and for a variety of other indications, such as colorectal perforation by foreign body, faecal incontinence or perianal abscess. Thirty-four emergency operations (16 ileostomy, 18 colostomy) and 42 elective operations (21 in each group) were performed.

At the primary operation the surgeon was requested to report the diagnosis, type of bowel preparation and the reason for construction of a temporary defunctioning stoma. Indications for construction of a stoma were divided into (1) anastomotic factors (17 patients each group), (2) general factors (15 ileostomy, 19 colostomy) and (3) deviation for various distal colonic or anorectal pathology (five ileostomy, three colostomy) (Table 2). The category 'anastomotic factor' included patients with proven anastomotic leakage at operation, anastomosis below the peritoneal reflection and patients with an unreliable or compromised anastomosis for reasons of technical difficulty, previous irradiation or a restricted view of the operative field. The category 'general factors' included patients with faecal contamination (extraluminal faeces in the pelvis), severe (faecal

Table 1 Patient characteristics

	Ileostomy ($n = 37$)	Colostomy ($n = 39$)
Mean (range) age (years)	63.2 (26–86)	64.7 (29–83)
Mean (range) weight (kg)	73.6 (45–123)	71.8 (52–115)
Sex ratio (M:F)	14:23	13:26
Diagnosis		
Malignancy	14	19
Diverticulitis	16	14
Other	7	6

Table 2 Indications for construction of a stoma

	Ileostomy (n = 37)	Colostomy (n = 39)
Anastomotic factors	17	17
Compromised anastomosis	9	5
Low anastomosis	3	2
Anastomotic leak	5	10
General factors	15	19
Faecal contamination	7	3
Peritonitis	3	9
Ileus	5	7
Deviation	5	3
Fistula	3	2
Other	2	1

or purulent) peritonitis and ileus. The distribution of various indications was similar for both groups.

Complications and deaths were recorded during the three phases of the study: at the time of stoma construction, during follow-up with the stoma and after stoma closure. Morbidity was divided into 'stoma-related' and 'general' complications. Stoma-related complications included stenosis, prolapse, necrosis, retraction, leakage of the stoma, parastomal hernia or fistula, and adjustment of clothes or diet to the stoma. General complications included those not directly related to the construction or presence of the stoma, such as abdominal sepsis or abscess formation.

Technique of stoma construction

The techniques of loop ileostomy and loop transverse colostomy were standardized amongst all five participating centres.

Stoma closure

Closure was conducted preferably 9–12 weeks after construction. After routine bowel preparation the stoma was closed by freeing it from the abdominal wall, and bowel continuity was restored by end-to-end anastomosis. During the postoperative period complications were recorded.

Follow-up

All patients were followed on a 3-monthly regular basis in the outpatient clinic for 1 year after stoma closure.

Statistical analysis

All data were entered in a computer database and analysed by an independent statistician. To test for differences between the two groups χ^2 test, *t* test and Mann–Whitney *U* test were used as appropriate. Differences were considered significant at $P < 0.05$.

Results

Complications after stoma formation, during follow-up and after closure of the stoma are reported. The course of the study is outlined in *Table 3*.

Complications after stoma construction

After stoma construction nine patients in the loop ileostomy group and one who had a loop colostomy had complications ($P < 0.01$) (*Table 4*). Complications were all serious and led to surgical reintervention. In four patients these complications were directly due to the presence of the ileostomy: prolapse, stoma leakage and small bowel ileus on two occasions. The other five patients had more general complications, such as abdominal abscess formation (two patients), rectal carcinoma causing fistula,

Table 3 Course of the study

	Ileostomy	Colostomy
Randomized and operated	37	39
Early death	5	1
Follow-up with stoma	32	38
Death during follow-up	1	4
Stoma not taken down	2	2
Stoma taken down	29	32
Death at closure	2	0
Follow-up without stoma	27	32
Total deaths	8	5

Table 4 Complications after stoma construction

	Ileostomy (n = 37)	Colostomy (n = 39)
Complications		
Stoma related	4	0
General	5	1
Total	9*	1
Deaths	5	1

* $P < 0.01$ versus colostomy group (χ^2 test)

abdominal wound dehiscence and acute femoral artery occlusion. The complication in the patient who had a colostomy was of general nature (abdominal abscess formation).

After stoma construction five patients with an ileostomy and one with a colostomy died (*Table 4*). Causes of death in the ileostomy group were abdominal sepsis in two, small bowel ileus in two (one of whom also had a myocardial infarction) and complications due to post-operative femoral artery embolism in one. The patient with a colostomy died from abdominal sepsis with abscess formation.

Complications during follow-up with the stoma

Stoma-related complications during follow-up are described in *Table 5*. Stoma prolapse was significantly more common after colostomy. Clothing had to be adjusted significantly more often in the presence of a colostomy. Stoma leakage and skin irritation were frequently reported in both groups. Because of the more excessive fluid and electrolyte loss through the ileostomy the diet had to be adjusted significantly more often in patients with a loop ileostomy. During the follow-up period before stoma closure, 30 complications were observed in the ileostomy group (0.9 per patient) and 40 in the colostomy group (1.1 per patient).

There were five deaths before stoma closure. One patient with an ileostomy died as a result of colonic liver metastases. Two patients who had a colostomy died from acute myeloid leukaemia, one from colonic metastases and one from local recurrence of rectal carcinoma before stoma reversal had taken place.

Twenty-nine of the 31 surviving patients with an ileostomy and 32 of the 34 with a colostomy underwent stoma closure.

Complications after stoma closure

Complications were reported in eight patients after ileostomy closure and three after colostomy closure

Table 5 Stoma-related complications during follow-up with stoma

	Ileostomy (n = 32)	Colostomy (n = 38)
Prolapse	1*	16
Retraction	4	1
Parastomal hernia	2	0
Parastomal fistula	1	2
Stenosis	0	1
Necrosis	0	1
Leakage	12	18
Skin irritation	3	9
requiring therapy	11	9
Adaptation of clothes	8*	22
Dietary measures	23*	4
Other	16	14
Total stoma-related complications	30	40

* $P < 0.01$ versus colostomy group (χ^2 test)

Table 6 Complications after stoma closure

	Ileostomy (n = 29)	Colostomy (n = 32)
Complications		
Ileus	2	1
Wound infection or haematoma	2	1
Fistula	2	1
Anastomotic leakage	1	0
Respiratory insufficiency	1	0
Total	8	3
Deaths	2	0

($P = 0.06$) (Table 6). All but one of the complications seen after stoma closure were related to the stoma reversal: ileus, wound infection or wound haematoma, enterocutaneous or colocutaneous fistula and anastomotic leakage.

Two patients died after ileostomy closure. One death was caused by anastomotic leakage and the other by respiratory insufficiency (due to lung metastases).

During outpatient clinic follow-up no significant morbidity was observed. No patient was lost to follow-up.

Discussion

This randomized study focuses on three different, important aspects of stoma care and stoma surgery: (1) the primary operation under elective and acute circumstances, (2) complications and problems of having a protective stoma and (3) complications of a second operation to reverse the stoma.

There are a few studies¹⁻⁷ comparing loop ileostomy with loop transverse colostomy, and these studies mainly focus on the primary operation. Of these studies two were randomized^{1,2} and showed no important differences between ileostomy and colostomy. The other studies³⁻¹⁰ were also essentially inconclusive. The present study was conducted in a group of relatively old patients in whom the impact of a stoma for daily life is potentially enormous. More stoma-related and general disease-related complications were observed in the ileostomy group. Ileostomy was a major source of complications

compared with colostomy. The incidence of significant complications, including death, due to loop ileostomy in this series is larger than that published in the literature. In two smaller prospective trials comparing loop ileostomy and loop colostomy^{1,2} no death from the stoma was experienced. In two large series describing temporary loop ileostomy after restorative proctocolectomy (203 and 296 ileostomies respectively)^{11,12} there were no deaths and the complication rate was low (7 per cent). The patients included, however, were much younger, a large proportion in one of these studies¹¹ was on steroids (67 per cent) and all underwent elective operation. In the evaluation of the present results, however, it is very difficult to separate morbidity related to the underlying disease from complications caused by adding a stoma to the procedure. Complications can be 'local' such as prolapse, retraction, parastomal fistula or herniation, stenosis, necrosis and leakage. Of these, prolapse is more often seen in patients with a colostomy. Complications can also be of a more general nature, such as wound infection, abdominal abscess formation and sepsis. These complications are not directly attributable to a specific type of defunctioning stoma. Since significantly more complications occurred in the ileostomy group, it can be postulated that a loop ileostomy might be less efficient for bowel decompression. It is questionable whether a stoma can protect patients from the complications of colorectal disease. However, this trial revealed a difference in perioperative complication and mortality rates. Perioperatively, seven patients in the ileostomy group died (five after construction and two after closure of the ileostomy) and one in the colostomy group. All of these patients needed one or more surgical reinterventions. Three of these deaths resulted from ileostomy-related complications (parastomal leakage, prolapse and small bowel ileus).

The interval between primary and secondary operation has not been studied previously. None of the complications noted in the period before stoma closure needed surgical reintervention. Prolapse was very common in the colostomy group, and was the reason for modifying clothing in almost all of these 16 patients. Leakage was observed in a high percentage in both groups. Ensuing irritation of the surrounding skin occurred more often than expected in the colostomy group. Adaptation of daily food intake and drinks was needed in two-thirds of the patients with an ileostomy and dehydration was effectively prevented by relatively simple means. Four patients did not have the stoma reversed, because they were frail. This is serious because these old patients consequently will be seriously restricted in lifestyle, and may even become restricted temporarily or permanently to a nursing home.

Closure of the stoma is, in general, an elective procedure under optimal circumstances. Nevertheless, many complications that are directly attributable to the former presence of a stoma were recorded. Taking down the ileostomy was accompanied by more serious complications than closure of the colostomy. Reversal of a loop ileostomy is not always 'just a local procedure'. The small bowel can be adherent to the abdominal wall as well as to adjacent loops with risk of damage to such loops. Because of the small entry to the abdomen, such damage can go unnoticed and lead to bowel leakage, abscess formation or intra-abdominal sepsis. Stenosis of the anastomosis, leading to (temporary) obstruction, can develop if the technique is not modified in the presence of luminal discrepancy. Repositioning of the anastomosis through a small hole can lead to torsion, obstruction and small

bowel ileus. Closure of a loop transverse colostomy is usually more straightforward.

Construction, as well as closure, of a loop ileostomy had frequent and more serious complications in comparison to loop colostomy. It is therefore concluded that loop ileostomy is not the stoma of choice for routine use for temporary decompression of the large bowel, although it is acknowledged that excellent results with loop ileostomy have been published from centres with considerable experience in routine use of this type of covering stoma in pelvic pouch surgery^{11,12}. Considering that complications frequently occur with both types of stoma, it is also concluded that use of a stoma should be restricted, and that attention should be paid to the technical aspects of a temporary stoma. It should always be kept in mind that at least 15 per cent of 'temporary' stomas will turn out to be permanent.

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Avoidable deaths still occur after large bowel surgery

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Background Postoperative death following large bowel surgery is relatively infrequent and no large study has analysed the cause of all deaths comprehensively and critically.

Methods In-hospital deaths following large bowel surgery in South-East Scotland were reviewed by independent assessors. The audit was confidential but not anonymous. Independent assessors' reports were returned to consultants.

Results The audit documented 187 deaths. The independent assessors noted an adverse event in 78 patients (42 per cent). Twenty-six deaths (14 per cent) occurred following an anastomotic leak. A further 43 deaths (23 per cent) occurred because surgery was delayed (17) or there was undue delay in making the initial diagnosis (12) or recognizing a developing complication (14). Consultants operated on only half the patients classed as American Society of Anesthesiologists grade IV or V, or undergoing a second or subsequent operation.

Conclusion Half the patients dying in this study had identifiable deficiencies in their management. There is a clear need for greater consultant input with critically ill patients.

Postoperative death following large bowel surgery is relatively infrequent and no individual surgeon or centre will have a large experience^{1–3}. Previous studies have not attempted to analyse the cause of death critically.

The Scottish Mortality Study, a forerunner to the Scottish Audit of Surgical Mortality, was a 2-year pilot project which studied all deaths that occurred on surgical wards in South-East Scotland. Data from the Scottish Mortality Study have been used to study the antecedent events and causes of death in a large cohort of patients.

Patients and methods

Between January 1992 and December 1993 inclusive, Scottish Mortality Study data for the regions of Lothian, Fife, Forth Valley, Borders, and Dumfries and Galloway were collected. Following the death of any patient in a surgical ward, the consultant surgeon, and when relevant the anaesthetist, were invited to complete separate parts of a mortality audit booklet. This included information on the patient's age, preoperative fitness, admission, preoperative and postoperative diagnosis, nature and timing of surgery, grade of surgeons consulted and actually operating, as well as use of intensive care or high dependency units. There was specific enquiry about adverse factors in the management of the case. Details of post-mortem requests were recorded, and, if performed, whether the autopsy contributed additional information. This audit booklet was returned to the central office where it was scrutinized by the audit coordinator (S.J.N.).

In almost all cases where death was not inevitable because of terminal disease the case notes and audit booklet were sent to one of a team of independent assessors for further review. There was no attempt to make the case notes anonymous. The initial mortality audit booklet and the independent assessor's report were scrutinized by the audit coordinator. Ultimately 118 items of coded data for each patient as well as short free-text entries were held on a central database. The anonymized independent assessors' reports were returned to the consultant. Selected

reports were published periodically and circulated to participating consultants.

This study retrieved data from the principal database on all patients undergoing a colorectal operation before death.

Results

In 1993 a total of 1012 mortality booklets were completed, a return rate of over 99 per cent⁴. One hundred and eighty-seven patients (56 per cent women) died following colorectal surgery. The mean age was 77 (range 21–94) years. In 69 (37 per cent) the initial operation was an elective procedure. All operations carried out with a greater degree of urgency were grouped together as emergencies. In 113 (60 per cent) the initial operation (Table 1) was for malignant disease (Table 2). At the initial

Table 1 Initial operation performed

Operation	Emergency	Elective	Total	LSA (%)*
Right hemicolectomy	21	15	36 (19)	15
Hartmann's procedure	28	4	32 (17)	7
Total colectomy	16	6	22 (12)	6
Defunctioning stoma	12	5	17 (9)	4
Sigmoid colectomy	5	8	13 (7)	6
Extended right hemicolectomy	10	0	10 (5)	3
Anterior resection	1	9	10 (5)	10
Bypass procedure	7	2	9 (5)	1
Abdominoperineal resection	1	6	7 (4)	5
Left hemicolectomy	3	3	6 (3)	3
Other resection	1	5	6 (3)	3
Other	13	6	19 (10)	37
Total	118	69	187 (100)	100

Values in parentheses are percentages. *Lothian Surgical Audit (LSA) documents all general surgical operations in Lothian and can therefore provide the denominator for this region (43 per cent of the study area). This column shows the proportion of the total number of operations that each procedure contributed to in Lothian

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operation 148 (79 per cent) had an American Society of Anesthesiologists (ASA) grade of III, IV or V (Table 3). Some 57 patients (30 per cent) had a second and 16 (9 per cent) a third operation; 93 per cent of these patients were graded ASA III or worse.

The single most significant cause of death, as determined by the independent assessors, was sepsis (Table 4). Two of the four patients with ASA grade I died from bowel-related sepsis (one following inadvertent damage and one following an anastomotic leak), with the others dying from pulmonary embolism and cerebrovascular accident.

In the assessors' opinion 141 adverse surgical events had contributed towards the death of 78 patients (42 per cent) (Table 5). This compared closely with the 139 adverse surgical events in 91 patients (49 per cent) documented by the surgeon. The correlation was close for objective events (e.g. anastomotic leak and delays in management). Some differences were noted for subjective issues such as whether or not the patient would have been better treated without surgery.

Anastomotic leakage was the single most important adverse event. Twenty of 26 leaking anastomoses (Table 5) were performed by a consultant. Delay before surgery and missed diagnosis were significant problems with emergency patients, whereas delay in recognizing a complication was a problem common to both elective and emergency cases. Seven of the eight 'wrong operations' were performed by the consultant. There was no evidence of failure of deep vein thrombosis prophylaxis in any of the nine deaths from pulmonary embolism.

The decision to undertake the initial operation was made by the consultant surgeon in 162 cases (87 per cent)

but did not increase for subsequent operations. One hundred and seven (57 per cent) of the initial operations were carried out by a consultant, but again did not increase for subsequent operations. Consultant surgeons and anaesthetists were responsible for only slightly more than half of patients graded ASA IV and V, or undergoing a second or third operation (Table 6). The majority of the 73 further procedures required a laparotomy and only five (7 per cent) were 'minor'. In four of eight patients where the surgeon was 'too inexperienced', the operation was undertaken without the trainee consulting a consultant or senior registrar. Consultants anaesthetized

Table 4 Principal cause of death as determined by the independent assessor

Cause of death	Age (years)		Operation		Total
	≥ 75	< 75	Emergency	Elective	
Sepsis	31	30	44	17	61 (33)
Progress of disease	10	16	14	12	26 (14)
Myocardial infarction	13	4	11	6	17 (9)
Cardiac failure	12	3	9	6	15 (8)
Bronchopneumonia	10	3	8	5	13 (7)
Cardiovascular accident	9	2	7	4	11 (6)
Aspiration	8	2	4	6	10 (5)
Pulmonary embolism	5	4	3	6	9 (5)
Multiorgan failure	2	6	6	2	8 (4)
Respiratory failure	2	2	2	2	4 (2)
Anastomotic leak*	1	1	1	1	2 (1)
Renal failure	1	1	2	0	2 (1)
General decline	1	1	2	0	2 (1)
Other	2	5	5	2	7 (4)
Total	107	80	118	69	187 (100)

Values in parentheses are percentages. *An additional 24 patients had anastomotic leak identified as an adverse factor but the principal cause of death was described otherwise, usually as sepsis

Table 2 Diagnosis at first operation

Diagnosis	Age (years)		Operation		Total
	≥ 75	< 75	Emergency	Elective	
Simple malignancy	27	19	12	34	46
Obstructed malignancy	34	15	33	16	49
Perforated malignancy	7	7	13	1	14
Other malignancy	1	3	1	3	4
Diverticular disease	22	14	30	6	36
Inflammatory bowel disease	2	8	5	5	10
Volvulus or intussusception	5	4	9	0	9
Ischaemia or infarction	2	5	7	0	7
Other	7	5	8	4	12
Total	107	80	118	69	187

Table 3 American Society of Anesthesiologists grade at initial operation

Grade	Emergency	Elective	Total
I	0	4	4 (2)
II	9	24	33 (18)
III	50	30	80 (43)
IV	46	11	57 (31)
V	11	0	11 (6)
Total	116*	69	185* (100)

Values in parentheses are percentages. *No data coded for two patients

Table 5 Adverse factors noted by assessor

	Emergency	Elective	Total
Objective			
Anastomotic leak	12	14	26
Wound dehiscence	4	5	9
Intensive care unit not used	4	2	6
Bowel damaged during operation	3	2	5
Postoperative bleeding	2	3	5
Excess intraoperative bleeding	2	2	4
Pneumothorax	1	1	2
Aspiration	2	0	2
Subjective			
Delay to surgery	16	1	17
Delay in recognizing complication	6	8	14
Missed diagnosis	11	1	12
Surgeon too junior	7	1	8
Wrong operation	5	3	8
Surgical technical error	0	3	3
Inadequate preoperative assessment	3	0	3
Patient better not treated?	3	0	3
Inadequate postoperative care	0	2	2
Miscellaneous	7	5	12
Total	88	53	141

Table 6 Grade of operating surgeon

	Consultant	Senior registrar	Registrar	Other	Total
First operation*	107 (58)	32 (17)	44 (24)	3 (2)	186
Second operation	29 (51)	9 (16)	15 (26)	4 (7)	57
Third operation	9 (56)	3 (19)	3 (19)	1 (6)	16
Emergency	55 (47)	27 (23)	32 (27)	3 (3)	117
Elective	52 (75)	5 (7)	12 (17)	0 (0)	69
ASA grade IV–V	40 (59)	14 (20)	13 (19)	1 (1)	68

Values in parentheses are percentages. *No data coded for one patient. ASA, American Society of Anesthesiologists

108 (58 per cent) of the first operations and 38 (52 per cent) of further operations.

Some 92 patients (49 per cent) were admitted into an intensive care unit at some stage. Seventeen patients were denied intensive care because there was no unit in their hospital, and four patients could not be admitted due to lack of intensive care beds. Only 34 patients (18 per cent) had an autopsy. When an autopsy was performed the surgeon considered that useful additional information had been gained in 80 per cent of cases.

Discussion

Death following large bowel surgery is now relatively rare. Contemporary audits report a 30-day mortality rate of approximately 5 per cent^{1,3} following surgery for colorectal cancer. It has been suggested that a further reduction will be hard to achieve because these patients are elderly, have significant medical comorbidity and often present as an emergency^{3,5}. However, this study suggests there is considerable scope for improvement as almost half the deaths were secondary to an adverse surgical event. It is clear that some of these adverse events were potentially avoidable. For example, it is difficult to argue that a death was unavoidable when the patient was undergoing a second or third operation (because of previous complications), or graded ASA IV or V and yet did not receive active input from either the consultant surgeon or anaesthetist. Consultants cannot defend deputizing the management of critically ill patients to juniors.

Anastomotic leakage remains the single most important adverse event. Given the wide variation in anastomotic leak rates between individual surgeons it has to be accepted that many are potentially avoidable^{1,3,6}. In the present study three-quarters of the anastomoses that leaked were performed by consultants, emphasizing the need for ongoing audit at all levels of seniority. The next commonest adverse events were delays of one sort or another. It is easy to recognize an unreasonable delay in retrospect but it is of concern that, even taking this into account, the assessors considered many were avoidable, a view normally supported by the surgeons themselves. This is a widespread problem. Both the Scottish Mortality Study, and subsequently the larger Scottish Audit of Surgical Mortality, noted that delays in diagnosis or management frequently contributed towards deaths in other surgical specialties⁴.

Often death was the end result of a chain of events. For example, 18 of 61 patients dying from sepsis had an anastomotic leak, and presumably the sepsis was secondary to the leak. Eight of ten patients dying from aspiration pneumonia did so following a second operation for a

surgical complication and therefore had two general anaesthetics close together.

As with the National Confidential Enquiry into Peri-operative Deaths (NCEPOD)⁷, the total surgical workload (the denominator) for the entire study area is not known and it is difficult to place these events in context. However, the Lothian Surgical Audit database can provide accurate figures for overall colorectal surgical workload in Lothian (an area representing 43 per cent of the Scottish Mortality Study data). In Lothian 2439 operations were performed over the 2 years. As in other studies^{8,9}, right hemicolectomy had a relatively high mortality rate, representing 14.8 per cent of all operations but 19.3 per cent of deaths, whereas anterior resection represented 10 per cent of all operations but only 5.3 per cent of deaths. In Lothian one-third of patients undergoing colorectal cancer resection present as an emergency³. This one-third of operations results in 63 per cent of the deaths, confirming that emergency surgery increases mortality nearly fourfold^{10,11}. In this audit, as in others, consultants were less frequently available for emergency cases^{3,12,13}.

Both the Scottish Mortality Study and the Scottish Audit of Surgical Mortality differ from the NCEPOD in that they are not anonymous and all deaths are reviewed. Despite the open nature of these audits the experience of both studies is that the clinical team responsible for the patients is prepared to identify areas of adverse management, and is often excessively self-critical. The final conclusion of the surgeon completing the mortality form and that of the independent assessor were usually similar.

This study reviewed 187 patients under the care of a large number of different consultant surgeons or anaesthetists working in 17 hospitals. In the authors' view the heterogeneous nature of the database meant that statistical analysis was not appropriate. Often several factors contributed to a patient's death and, while assessors might agree that several objective events occurred, they may not attach the same degree of importance to each event. There would obviously be greater variation in the assessment of more subjective criteria.

It has been suggested that retrospective studies of preventable deaths are flawed by the subjectivity of assessment¹⁴. Certainly caution must be exercised when using such data as a hard measure of quality of care, but individual peer review remains the mainstay of morbidity and mortality audit at a unit level and surgeons must recognize and acknowledge their shortcomings if anything is to be gained from the unexpected death of a patient.

In conclusion, this study has shown that a simple area-wide audit can identify areas of inadequate care that are potentially correctable. The elderly and frail may survive major surgery but rarely survive a major complication. Nearly half the patients dying after operation had identifiable deficiencies in their management and there is a clear need for greater consultant input.

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Laparoscopic management of acute small bowel obstruction

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Background Laparoscopic management of acute small bowel obstruction is hypothetically attractive but little is known of its clinical potential.

Methods A retrospective study was undertaken of patients with acute small bowel obstruction requiring surgery, managed by a laparoscopic unit (LU; $n = 69$) and a general unit (GU; $n = 70$).

Results Laparoscopy was performed in 55 patients (80 per cent) in the LU compared with ten (14 per cent) in the GU. Laparoscopic surgery completed treatment in 31 patients (45 per cent) in the LU and assisted in a further 15 (22 per cent). Patients treated laparoscopically were discharged earlier than those treated by laparotomy (median 3 (range 1–15) *versus* median 8 (range 1–46) days). Patients treated laparoscopically had a higher chance of early unplanned reoperation than those treated by laparotomy (five of 35 *versus* four of 88) ($P < 0.05$).

Conclusion Laparoscopy can be performed in a high percentage of patients requiring surgery for acute small bowel obstruction. Hospital stay was reduced but the risk of early unplanned reoperation was increased in patients managed laparoscopically.

After an appropriate trial of conservative management, laparotomy and adhesiolysis with or without bowel resection is the traditional operative management for adhesive small bowel obstruction. As such surgery rarely involves removal of large specimens it would be a reasonable aim to deal with obstructing adhesions laparoscopically. A few reports of laparoscopic management of acute small bowel obstruction have been published^{1–8} but the technical difficulties of handling adhesions and dilated intestine are discouraging. In addition the unpredictable nature of adhesions may make case selection difficult. It is therefore unclear if laparoscopic techniques have a significant role to play in the management of small bowel obstruction requiring surgery.

The results of a policy of such laparoscopic management are described and compared with those obtained by a more traditional technique.

Patients and methods

Patients undergoing operative management of acute small bowel obstruction by the authors and by other general surgeons at this hospital between July 1993 and October 1995 were identified from a hospital discharge database, surgical unit audit data and a prospective database established to study patients undergoing laparoscopic surgery. Patients with a preoperative diagnosis of acute small bowel obstruction but with no definite preoperative cause identified, or presumed adhesion obstruction, were identified by case-note review and are the subject of this study. The operation note was reviewed and the cause of the obstruction was classified into one of five categories: general adhesions, local adhesions, obstructing band, tumour or other (hernia, Crohn's disease, foreign body).

Previous abdominal surgery was recorded as was previous abdominal malignancy. Duration of surgery was recorded prospectively in the case notes. Length of postoperative stay was recorded, based on date of discharge or date of transfer to rehabilitation geriatric care services. Complications were recorded, with particular attention to abdominal complications and those requiring reoperation. Surgery was defined as completed laparoscopically, laparoscopically assisted (when a localized incision was made), laparoscopic converted or

laparotomy. The surgical procedure was summarized as one or more of the following: adhesiolysis, resection or bypass.

Patients managed by the authors, a specialist laparoscopic group, were compared with those managed by other general surgeons.

Laparoscopic operative technique

Patients were positioned supine with an indwelling catheter and large-bore nasogastric tube. Pneumoperitoneum was established with an open technique, either via the umbilicus or by careful dissection with tissue splitting away from previous scars. Initially staff and equipment were positioned with the surgeon on the patient's left and the monitor by the patient's right hip. Once the peritoneal cavity had been entered ports were placed to allow adhesiolysis for access to the right iliac fossa. Where possible distended bowel was not handled and dissection was aimed at exposing collapsed distal bowel. The distal collapsed bowel was then walked between bowel graspers until the point of obstruction was identified. Adhesiolysis utilized combined sharp and blunt dissection with either monopolar or bipolar diathermy. Adhesions were divided until the obstruction was relieved. Often a band amongst adhesions was divided only without extensive adhesiotomy. Appropriate patient positioning was used to gain adequate exposure, and where necessary the screen and surgical staff moved positions to aid dissection. Bowel requiring resection was exteriorized through an appropriately positioned incision, resected and reanastomosed. Obstructions requiring enterenterostomy were managed by laparoscopic stapling when possible or via an appropriately placed incision and external anastomosis.

Statistical analysis

Data were analysed using either χ^2 test or Mann–Whitney U test. Statistical significance was presumed if $P < 0.05$.

Results

One hundred and thirty-nine patients were studied. Sixty-nine were managed by the laparoscopic surgical unit (LU) and 70 by the general unit (GU). The patients were of a similar age and had a similar previous surgical history (Table 1).

Laparoscopy was attempted in 55 (80 per cent) of 69 patients in the LU and ten (14 per cent) of 70 in the GU

Table 1 Comparison of patients treated in a laparoscopic unit and a general unit

	Laparoscopic unit	General unit
Total no. of patients	69	70
Mean (range) age (years)	59.5 (15–94)	58.2 (16–93)
Previous abdominal surgery*	53 (77)	58 (83)

*Values in parentheses are percentages

Table 2 Method of surgical treatment

	Laparoscopic unit	General unit	Total
Total no. of patients	69	70	139
Laparoscopy	55 (80)	10 (14)	65
Treatment completed laparoscopically	31 (45)	4 (6)	35
Laparoscopically assisted	15 (22)	1 (1)	16
Laparoscopic converted	9 (13)	5 (7)	14
Laparotomy	14 (20)	60 (86)	74

Values in parentheses are percentages. There was a significant difference in all categories ($P < 0.05$; χ^2 test)

Table 3 Patients requiring early reoperation

Unit	Age (years)	Operation type	Operative findings	Reason for reoperation	Total hospital stay (days)
GU	73	Laparotomy	Adhesions	Unrecognized operative perforation	3 (died)
GU	24	Laparotomy	Adhesions	Reobstruction day 10	33
GU	51	Laparotomy	Adhesions	Sepsis day 7	14
LU	70	Laparoscopic converted	Tumour	Reobstruction day 18	24
LU	59	Laparoscopy	Band	Reobstruction day 11	3
LU	48	Laparoscopy	Local adhesions	Reobstruction day 21	10
LU	48	Laparoscopy	Band	Band site perforation day 4	7
LU	78	Laparoscopically assisted	Local adhesions	Peritonitis day 3	40 (died)
LU	69	Laparoscopy	Tumour	Perforation	12
LU	36	Laparoscopy	Local adhesions	Failed to settle; two laparotomies performed	28

LU, Laparoscopic unit; GU, general unit

Table 4 Postoperative deaths

Unit	Age (years)	Operative findings	Operative procedure	Cause of death
LU	78	Adhesions	Laparoscopically assisted (resection)	Sepsis and MOF day 40
GU	80	Adhesions	Laparotomy (adhesiolysis/perforated)	CVA day 25
GU	74	Tumour	Laparotomy (bypass/resection lasting > 3 h)	Respiratory failure day 1
LU	71	Tumour	Laparotomy (bypass)	Respiratory failure day 1
GU	83	Tumour	Laparotomy (adhesions)	MOF day 8
GU	36	Tumour	Laparotomy (bypass)	Renal failure day 20
GU	93	Internal hernia	Laparotomy	Respiratory failure day 5
GU	73	Adhesions	Laparotomy (adhesiolysis/perforated)	Cardiac failure/sepsis day 2
LU	85	Band	Laparotomy (adhesiolysis)	Respiratory failure day 8
GU	81	Local adhesions	Laparotomy (adhesiolysis/perforated)	MOF day 60

LU, Laparoscopic unit; GU, general unit; MOF, multiple organ failure; CVA, cerebrovascular accident

($P < 0.01$). The procedure was completed laparoscopically in 31 patients (45 per cent) in the LU and four (6 per cent) in the GU ($P < 0.01$). In a further 15 patients (22 per cent) in the LU the procedure was classified as laparoscopically assisted surgery and in nine (13 per cent) the procedure was converted to a full laparotomy. Therefore in 46 of 55 (84 per cent) patients undergoing laparoscopy in the LU laparoscopy altered management (Table 2).

The LU treated a higher proportion of patients classified as having local adhesions or a localized band adhesion than the GU (44 (64 per cent) versus 34 (49 per cent)) and fewer patients with peritoneal tumour (seven (10 per cent) versus 13 (19 per cent)) (P not significant).

Ten patients (7 per cent) required further unplanned abdominal surgery within 30 days of the original operation. Five of the 35 patients who had procedures completed laparoscopically required early reoperation compared with four of 88 patients (4.6 per cent) having a full laparotomy ($P < 0.05$). Details of reoperated patients are summarized in Table 3.

Patients treated laparoscopically stayed in hospital for a shorter time than those treated initially by laparotomy (Fig. 1).

The median duration of operation was 64 (range 15–180) min for operations completed laparoscopically, 83 (range 25–160) min for laparoscopically assisted procedures, 110 (range 50–250) min for laparoscopic converted procedures and 83 (range 25–180) min for patients having an initial laparotomy.

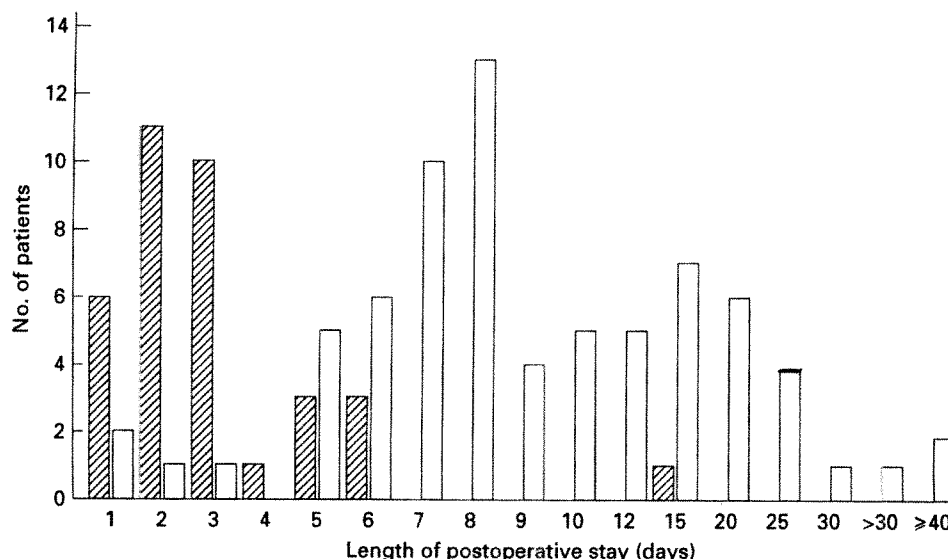


Fig. 1 Postoperative stay for patients treated entirely laparoscopically (▨) and for those having a full laparotomy (□). Postoperative stay was significantly shorter in patients treated laparoscopically ($P < 0.05$; Mann-Whitney U test)

Ten patients died during the postoperative period in hospital, the majority of whom had undergone laparotomy (Table 4).

Discussion

This series compares laparoscopic surgical management of patients with acute small bowel obstruction with a contemporary group of patients managed in a more traditional manner. The laparoscopic group has extensive experience of advanced laparoscopic surgical procedures and managed a progressively higher proportion of its patients with an initial laparoscopy.

Laparoscopy was attempted in 80 per cent of all patients in the LU and in 20 of the last 21 patients treated. Thirty-one patients (45 per cent) in the LU group patients were treated totally laparoscopically. Others have suggested that only 25 per cent of these patients will be suitable for laparoscopic therapy^{1,2}, although some have reported use of laparoscopy in almost 100 per cent of patients². Levard *et al.*² completed 12 of 25 operations laparoscopically. It is difficult to predict which patients will be suitable for laparoscopic therapy and an initial laparoscopic approach is justifiable for all patients in a LU.

Open cannulation allowed safe peritoneal access in this series. Blind cannulation is not appropriate in acute small bowel obstruction as trocar perforation has been reported in 3.7 per cent of cases².

Handling of dilated bowel should be kept to a minimum. Even with laparoscopic bowel graspers the danger of injury to dilated bowel is high.

The patients managed laparoscopically were discharged earlier than those managed by laparotomy. However, the patients managed laparoscopically showed a trend to less severe disease compared with those managed by laparotomy and, in view of the retrospective and non-randomized nature of this clinical study, such results must be viewed with caution. It is, however, unusual for patients undergoing laparotomy for acute small bowel

obstruction to leave hospital within 72 h of surgery; in the present study 27 patients treated laparoscopically left hospital within 3 days (Fig. 1).

There was a significantly higher incidence of early reoperation in the laparoscopically treated group compared with those having laparotomy. This may be a reflection of the technical difficulties of laparoscopic surgery for small bowel obstruction and mirrors the experience reported previously. Levard *et al.*² reoperated on three of 12 patients and Francois *et al.*¹ reoperated on six of 17 for reobstruction although it is not clear when during follow-up this occurred. Despite the need for reoperation the overall results were encouraging.

The mortality rate for the whole patient group was 7 per cent which is comparable to other groups' experience of such a broad group of patients⁹. As might be expected death was commoner in patients who were elderly and who had peritoneal tumour. The mortality rate was higher in those who had laparotomy rather than laparoscopy. This may reflect an advantage of the laparoscopic approach or the less severe disease in those having laparoscopy.

Eypasch *et al.*⁸ have recently advised against laparoscopy for acute small bowel obstruction. The present study demonstrates that with an experienced team laparoscopy may have a useful role in the surgical management of acute small bowel obstruction. However, this surgery is difficult and complications requiring reoperation are more common.

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Dynamic graciloplasty for severe anal incontinence

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Background The surgical options for the treatment of anal incontinence where standard procedures have failed include transposition of striated muscles, primarily gracilis and gluteus maximus, and implantation of artificial sphincters. Due to a high proportion of fatigue-prone fibres in striated muscles, the results of transposition without stimulation have been disappointing. This study presents the results of stimulated graciloplasty in 13 patients with severe anal incontinence in whom other surgical procedures had failed.

Methods The gracilis muscle was transposed around the anal canal according to a previously described technique. Eight weeks later the intramuscular electrodes were implanted into the gracilis at the site of the nerve entry and a neurostimulator was placed in a subcutaneous pocket in the abdominal wall. The patients were followed from 7 to 27 months.

Results Six patients obtained satisfactory continence and five showed marked improvement. Two patients were considered failures. Rectal evacuation problems occurred in three patients, in one so severe that the patient, in spite of satisfactory continence, considered the treatment a failure.

Conclusion Dynamic graciloplasty is a viable option in carefully selected patients with severe anal incontinence where other methods have failed.

The prevalence of persistent incontinence in Europe and in the USA is around 2 per cent^{1,2}. In a number of these patients conservative measures will result in a satisfactory improvement but the majority will at some stage need surgical treatment. The aim of the different surgical procedures is to create acceptable control of bowel movements and avoid enterostomy, the end stage surgical treatment for incontinence.

Traumatic anal incontinence may be successfully treated by external sphincter reconstruction in 80–90 per cent of patients^{3–5}. Surgical treatment of idiopathic incontinence will only result in satisfactory faecal control in approximately 50 per cent of patients, perhaps even less after 2–3 years^{6,7}.

In patients for whom these standard surgical procedures fail and in patients with extensive sphincter destruction or severe nerve damage, alternative procedures include transposition of the gracilis or gluteus maximus muscle, implantation of an artificial anal sphincter and implantation of a neuroprosthesis^{8–14}.

Transposition of an unstimulated gracilis muscle has improved faecal control in some patients, but satisfactory results are seen only in a few^{15,16}.

The main reason for the unsatisfactory results of gracilis transposition is probably that skeletal muscle is unable to maintain sustained contraction due to preponderance of type II muscle fibres that can only provide forceful contraction for a short time¹⁷. Animal, as well as human, studies have shown that electrical stimulation improves the function of a graciloplasty^{18,19}. This has prompted the implantation of an electrical stimulator which by continuous stimulation through electrodes implanted into the muscle transforms the fatigue-prone type II fibres into fatigue-resistant type I fibres¹⁹. Results from the two groups who have developed this technique of dynamic graciloplasty, although with different types of stimulators and electrodes, have been encouraging^{20,21}.

The present authors report herein the results of gracilis transposition combined with implantation of intramuscu-

lar electrodes connected to a neurostimulator in 13 patients with severe anal incontinence all of whom previously had been treated surgically for anal incontinence.

Patients and methods

Patients

Thirteen patients (ten women, three men; median age 48 (range 26–74) years) underwent dynamic graciloplasty.

The aetiology and previous operations for anal incontinence are shown in Table 1. There were three patients (one woman, two men) with anal atresia who had all undergone anoplasties as infants. The woman still had the anal orifice located in the vaginal vestibulum and one of the two male patients had previously undergone gluteus maximus transposition with unsatisfactory result; the other male patient had serious aggravation of incontinence after a subtotal colectomy for chronic abdominal pain with faecal impaction in the right colon. One patient with traumatic incontinence following a traffic injury and one with anal atresia had an enterostomy.

The continence score on a modified Williams scale¹⁷ is shown in Table 2. Anal manometry, rectal compliance and electromyography were performed as described previously²². Pre-operative anorectal physiology parameters are shown in Table 3.

Surgical technique

The technique of gracilis transposition has been described previously⁹. In short, the gracilis muscle on one side (left or right after the patient's choice) was mobilized either through one long or two short incisions to its insertion into the tibial tuberosity, and the distal tendon was divided. Proximally the neurovascular bundle was isolated and left intact, and the muscle was transposed around the anal canal through two small incisions at 90° and 270°; finally, the tendon was fixed to the ischial tuberositas on the opposite side with 1/0 non-absorbable sutures.

Eight weeks later intramuscular electrodes were implanted into the muscle at the site of the nerve entry and through a subcutaneous tunnel connected to a neurostimulator (Itrel II; Medtronic, Minneapolis, Minnesota, USA) which was placed in a subcutaneous pocket in the abdominal wall. The stimulator was programmed telemetrically to the lowest amplitude which, during implantation, was found to give sufficient contraction. The

Table 1 Aetiology and previous surgery for faecal incontinence

Aetiology	Previous surgery				Total
	Sphincteroplasty	Postanal repair + anterior perineoplasty	Gluteus maximus transposition	Enterostomy	
Obstetric lesion	6	0	0	0	6
Other trauma	1	0	0	1	12
Idiopathic	0	2	0	0	2
Anal atresia	0	0	1	2	3
Total	7	2	1	3	13

muscle was trained with cyclical stimulation with increasing on-time until continuous stimulation was started after 8 weeks. The patient could switch the stimulator on and off with an external magnet.

The patients with a colostomy had this closed 4 weeks after implantation of the stimulator. The female patient with a vaginal vestibular anus had the bowel displaced to the perineum and the vagina reconstructed in connection with the graciloplasty.

Antibiotic prophylaxis consisted of gentamicin 240 mg and metronidazole 1 g during operation. After implantation of the stimulator and electrodes, prophylaxis was extended to 3 days with gentamicin 240 mg daily and metronidazole 500 mg three times daily. Changes in anal pressure were estimated by the Wilcoxon signed rank test for pair differences. The study was approved by the ethics committee of Copenhagen County.

Results

Follow-up was 7 to 27 months after the initiation of continuous stimulation. Continence score at follow-up is

Table 2 Scoring for faecal incontinence before and after surgery

Before operation (n)	After operation (n)	Score	Symptoms
0	3	1	Continence with regard to solids, liquids and flatus
0	3	2	Continence with regard to solids and liquids, but not to flatus
0	5	3	Continence with regard to solids, but occasional incontinence of liquids
0	1	4	Occasional episodes of incontinence of solids
13	1	5	Frequent episodes of incontinence of solids and liquids

Continence score given on a modified Williams scale¹⁷

Table 3 Preoperative anorectal physiology

Parameters	
Resting anal pressure (cmH ₂ O)	18 (12–36)
Squeeze anal pressure (cmH ₂ O)	47 (21–65)
Maximum EMG amplitude during squeeze (μV)	101 (25–160)
Rectal MTV (ml)	133 (78–277)
Rectal compliance (Δv/Δp)	3.7 (1.0–9.8)

Values are median (range). EMG, electromyography; MTV, maximum tolerable volume; Δv, volume increase; Δp, pressure increase

shown in Table 2. Six patients obtained satisfactory continence (scores 1 and 2) and five patients had improved continence with a change from score 5 to 3. Only two patients were considered complete failures. Results of anal manometry are shown in Table 4. There was a significant increase in resting anal pressure from a median of 18 (range 12–36) cmH₂O before operation to 30 (range 20–80) cmH₂O at follow-up with the stimulator switched on ($P < 0.01$), and an increase in maximum squeeze pressure from 47 (range 21–65) to 61 (range 25–41) cmH₂O ($P < 0.01$). To maintain sufficient contraction, the voltage of the stimulator had to be increased during the follow-up period in nine patients and ranged from 1.6 to 4.8 volts.

Side-effects were seen in ten patients: pain at the stimulator site in five, infection around leads in one, impaired rectal evacuation in three, and perianal pain in one patient. Three patients who had not experienced emptying problems before operation developed impaired rectal evacuation. Judged by physical examination there was no anatomical obstruction, which was confirmed by defaecating proctography. One patient had an infection around the leads which was treated by revision and systemic and local antibiotics. There were no infections around the stimulator. Revisional procedures were performed in nine patients. As a result of pain the stimulator was repositioned in five patients, in one patient by creating a new subcutaneous pocket and in four (all slim) by positioning the stimulator below the rectus muscle. One patient still complained of pain, and was treated by

Table 4 Anal manometry in individual patients before and after operation (cmH₂O)

Patient no.	Preoperative anal pressure		Postoperative anal pressure	
	Resting	Squeeze	Resting	Squeeze
1	18	41	21	61
2	19	28	80	103
3	15	21	30	51
4*	20	25	25	25
5	31	52	50	68
6	12	41	30	58
7*	12	41	20	42
8	18	47	40	104
9	36	60	75	93
10	36	56	75	86
11	15	41	30	41
12	20	36	20	46
13	12	65	40	110

*Failure (continence score of 4 or 5)

lidocaine blockade with some effect. One patient had revision of the leads due to infection, two patients who were incontinent for fluid faeces and whose muscle did not close the anal canal completely during maximum stimulation had the muscle tightened by shortening the tendon. This had a satisfactory effect in one patient, but not in the other. One patient with anal atresia developed a mucosal prolapse with soiling; the prolapse was excised and the soiling almost ceased.

The overall patient satisfaction with defaecatory function was evaluated on a visual analogue scale from 1 to 5 where 1 is 'as poor as before the operation' and 5 is 'completely satisfactory result with no interference of defaecation with daily life'. Five patients found the result satisfactory (groups 4 and 5), all having a postoperative continence score of 1 or 2. One patient with satisfactory continence (score 2) was dissatisfied with the overall result due to difficulty of rectal evacuation. The five patients with improved continence (continence score 3) all responded with a satisfaction score of 3.

The reasons for decreased patient satisfaction apart from unsatisfactory continence were obstructed defaecation in three patients, persisting pain at the stimulator site in two, and perianal pain in one.

Discussion

As the authors have a long experience in performing gracilis transposition⁹ their results are not affected by any learning curve, and consequently should be representative of what may be obtained by dynamic graciloplasty in severely incontinent patients where other surgical methods have failed.

Their results are less favourable than those of Baeten *et al.*²¹ who, with the same technique obtained satisfactory continence (scores 1 and 2) in 75 per cent of patients. This may be due to different patient selection as only 39 of 52 patients in the series by Baeten and colleagues had previously undergone other types of incontinence surgery. They included patients with a postoperative continence score of 3 among the failures whereas the present authors considered that a change from a score of 5 to 3, although not a satisfactory result, represented an improvement. Consequently, only two patients in the present series were considered complete failures.

The pressure increase obtained in this study compares well with that reported by Baeten *et al.*²¹ but is lower than that obtained by direct nerve stimulation¹⁷. It is not surprising that stimulation of the nerve trunk gives better contraction than intramuscular stimulation of the nerve branches. The intramuscular placement of the electrode, however, also minimizes the risk of nerve damage as it allows implantation to be performed as a secondary procedure in patients who previously have had gracilis transposition.

Part of the effect of the gracilis wrap may be a lengthening of the anal canal high pressure zone; this length, however, is difficult to measure due to the asymmetry of the wrap.

There was some discrepancy between continence score and the patient's overall view of their quality of life following the operation. The most serious factor, apart from unsatisfactory continence, contributing to a reduction in patient satisfaction with the operation was impaired rectal emptying. This was a serious problem in three patients although no anatomical obstruction by the

muscle wrap was found. Defaecating proctography confirmed the impaired rectal emptying without demonstrating any anatomical abnormalities. None of the patients recalled having suffered from rectal emptying problems before the operation. Neither Baeten *et al.*²¹ nor Williams *et al.*¹⁷ mention this complication, but in a preliminary report of four patients, impaired rectal evacuation was a severe problem in two²³. The nature and reason for this complication was unknown, but obstructed defaecation may have preceded the incontinence without being realized by the patient years later. Objective demonstration of impaired rectal evacuation by enema tests or defaecography before operation may be impossible in severely incontinent patients because of their inability to retain fluid or contrast in the rectum. High maximum tolerable rectal volume (MTV) before operation may be a risk factor for development of impaired rectal evacuation²⁴, but none of the patients in this series had MTV outside the normal range, the highest being 277 ml.

Preoperative anal pressure did not predict the result with respect to postoperative continence, whereas the two patients who were considered failures had almost no increase in maximum squeeze pressure after the operation (Table 4).

Infection was only a minor problem in this series as there was only one case of infection around the leads and none in relation to the stimulator, whereas in the series by Baeten *et al.*²¹ seven of 52 patients had infection around the stimulator and leads which required removal of the device. In the present series pain at the stimulator site required repositioning of the device in five patients which may suggest that in thin patients the stimulator primarily should be placed in the rectus sheath and not in a subcutaneous pocket.

In conclusion, dynamic graciloplasty is a viable option in carefully selected patients with severe anal incontinence where other methods have failed or are unsuitable. The procedure can be performed with only minor complications and does not require diverting colostomy; however, only about one-half of patients will have a completely satisfactory result.

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Radical and nerve-preserving surgery for rectal cancer in the Netherlands: a prospective study on morbidity and functional outcome

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Background Operative procedures for primary rectal cancer from Japan combine pelvic nerve-preserving techniques with radical tumour resection to ensure optimal local tumour control with minimal bladder and sexual dysfunction. A prospective study was undertaken to evaluate morbidity and functional outcome of such a technique in Dutch patients.

Methods Forty-seven patients were operated on by a Japanese surgeon. Postoperative course was monitored. Voiding and sexual function were analysed using questionnaires completed by patients.

Results After operation, only prolonged paralytic ileus (five of 47 patients) and perineal wound dehiscence (five of 18) occurred more frequently than reported in literature. There were no deaths. No patient developed urinary incontinence. Three of 11 women and 19 of 30 men were sexually active. Two men were impotent after operation. Impotence was related to sacrifice of the inferior hypogastric plexus ($P = 0.037$). Preservation of the superior hypogastric plexus was crucial for ejaculation ($P = 0.003$).

Conclusion A relationship between sacrifice of specific nerve structures and accompanying dysfunction was established. The nerve-preserving technique yields good results in terms of morbidity and functional outcome, and should be considered for adoption as a standard surgical procedure for primary rectal cancer.

In the quest to improve the results of surgical treatment for primary rectal cancer, many authors advocate surgical techniques directed to more radical excision of the tumour^{1–3}. Criticism of more extended resection focuses on the increased postoperative complication rates and raised mortality figures. However, very few studies are available in which such morbidity for radical surgical techniques has been studied meticulously^{4,5}. Furthermore, conventional surgery for rectal cancer is associated with specific morbidity such as bladder and sexual dysfunction^{6,7}. Operative techniques from Japan combining pelvic nerve-preserving techniques with radical resection to ensure optimal local tumour control with minimal impairment of sexual function and bladder function seem promising⁸. A prospective study has been undertaken in which Dutch patients with primary rectal cancer were operated on by a noted Japanese surgeon (Y.M.), who performed a surgical technique specifically directed to the preservation of the pelvic nerves, in combination with a radical resection of cancer along strictly described anatomical dissection planes. The primary endpoints were morbidity, death, voiding and sexual function.

Patients and methods

Patients with histologically proven primary adenocarcinoma of the rectum located within 15 cm of the anal verge were eligible for the study. Data on patient characteristics, tumour classification, surgical factors and pathology were recorded. From November 1994 to February 1995, 47 patients from 24 hospitals

throughout the Netherlands were entered in the study. All patients were operated upon by Y.M. assisted by the local Dutch colorectal surgeon. Some 33 patients were men and 14 women, and the mean(s.d.) age was 63.4(12.3) (range 30–85) years. Twenty-eight patients underwent a sphincter-saving procedure (SSP), 18 abdominoperineal resection (APR) and in one case a Hartmann's procedure was performed. In 42 patients the distance between the lower tumour edge and the anal verge was measured at rigid endoscopy; for patients who underwent SSP the mean(s.d.) distance was 7.8(3.2) (range 3–15) cm and in the APR group it was 2.1(1.3) (range 0–5) cm. Tumours were staged according to Astler and Collier's classification⁹ with the following distribution: A, one patient; B1, nine; B2, 17; C1, one; C2, 16; and D, three.

Surgical anatomy of the pelvic autonomic nervous system

The superior hypogastric plexus (SHP) is a fenestrated network of fibres anterior to the lower abdominal aorta. The hypogastric nerves exit bilaterally at the inferior poles of the SHP which lie at or just below the level of the sacral promontory. The network of nerve structures is located in between the endopelvic fascia and the peritoneum. The hypogastric nerves unite the SHP with the inferior hypogastric plexus (IHP) or pelvic plexus bilaterally. The IHP has connections with the sacral roots from S3 and some contributions from S4 and S2 (Fig. 1).

The surgical goal in this study was to operate with an optimal balance between radical surgery for cancer on the one hand, and preservation of nervous structures on the other. However, the surgical technique in this study was more focused on maximum nerve preservation than the standard procedure in Japan^{8,10}. Only in patients with advanced tumours, in whom preservation of nerves was judged at operation by both Y.M. and the local Dutch surgeon to possibly compromise a radical excision of the tumour, were specific nerve structures sacrificed deliberately. The SHP or unilateral IHP was therefore completely removed together with the tumour in some cases.

Surgical technique

Mobilization of the left colon was performed in a standard fashion. The retroperitoneal space was opened, both ureters were identified and carefully mobilized, and the common iliac vessels were cleared of overlying tissue. The retroperitoneum just below the horizontal part of the duodenum was dissected, and the inferior mesenteric vein was identified and ligated at the level of the horizontal part of the duodenum. More caudally, the inferior mesenteric artery (IMA) was identified and ligated at its origin. If the SHP was to be preserved, it was first identified in the interiliac trigone, between the pedicle of the superior rectal vessels and the point just distal to the aortic bifurcation. After that, the IMA was not ligated flush with the aorta, but 1–2 cm lower, to avoid injury to any preaortic sympathetic nerve fibres. Anterior to the promontory, the avascular plane between the proper rectal fascia and the parietal fascia was entered by incising the visceral fascia between the two hypogastric nerves. The two bundles of the hypogastric nerve which run close to the proper rectal fascia along the pelvic wall were gently brushed laterally. Under direct vision, the mesorectum was mobilized in the medial presacral plane by sharp dissection using a long pelvic retractor. The plane of excision was completely outside the mesorectum and continued to the level of the coccyx¹. In the case of sacrifice of the SHP, the retrorectal dissection was carried out along the parietal fascia under direct vision of both the middle sacral and internal iliac vessels.

Identification and preservation of the IHP involved a strict sequence of steps with important landmarks to be identified. First the piriform muscle was identified and its overlying endopelvic fascia excised. The nervi erigentes could subsequently be identified as they emerged from behind the muscle. Working

upward, these nerves could be followed to where they entered the IHP and the exact location of the IHP determined. Continuing the dissection on the lateral side, the hypogastric nerve could be followed and the IHP freed from the rectum using a combination of very careful cautery, suction and blunt dissection. Branches which emerged from the IHP to the rectum were dissected and the IHP was gently pushed laterally. The IHP was finally freed from the rectal wall and thus preserved. Subsequently, anterior dissection was performed keeping Denonviller's fascia on the rectal side. In patients with mid and low rectal tumours the entire mesorectum was excised. APR was performed for very low tumours.

Assessment of postoperative morbidity and functional outcome

Immediately after the operation, the extent of nerve preservation of each patient was described on a pro forma. Participating surgeons completed forms that required detailed description of the postoperative course of the patients. All patients were requested to fill out a baseline questionnaire in the week before the operation. The forms consisted of a validated quality of life questionnaire, the Rotterdam Symptom Checklist¹¹, supplemented by specific questions regarding frequency of urination, incontinence, sexual activity for all patients, dyspareunia for women, and impotence, hardness and duration of erection and ability to ejaculate for men. Three and 6 months after surgery, patients received a subsequent follow-up questionnaire at their home address. Data were stored in a Medical Research Data Management program and statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) PC + 4.1 program (SPSS, Chicago, Illinois, USA). For

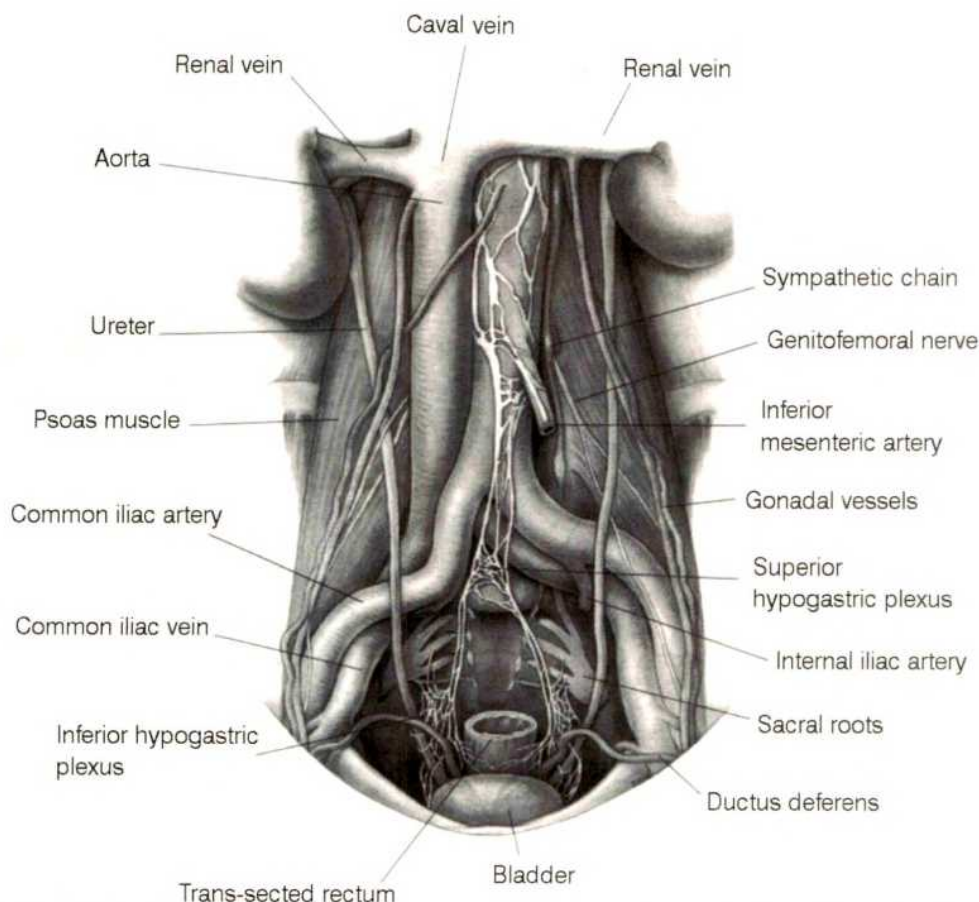


Fig. 1 Diagram of the abdominal and pelvic autonomic nervous system. Reproduced with permission from Steup WH. Colorectal cancer surgery with emphasis on lymphadenectomy. Thesis, Leiden, The Netherlands, 1995

comparison of means Student's *t* test was applied. For population proportions χ^2 test for fourfold tables was used.

Results

The mean(s.d.) operating time was 185(50) min (range 1 h 40 min to 5 h). Blood loss ranged from 100 to 3000 ml with a mean(s.d.) of 730(560) ml. Of 47 patients, 25 had in-hospital complications (Table 1). In five patients re-operation was needed to treat complications. In three patients anastomotic leakage occurred, two of whom required a temporary colostomy. The other patient developed a pelvic abscess, and the surgeon reoperated, dismantled the anastomosis and constructed an end colostomy. The other indications for surgical re-intervention included one abdominal and one perineal wound dehiscence. All other complications were treated conservatively. Five patients had a delay in returning to a normal diet of mean 18 (range 12–25) days, compared with 7 days in the other patients ($P < 0.001$). These five patients are classified as having 'paralytic ileus' in Table 1. All cases resolved spontaneously. Postoperative stay ranged from 8 days in a patient with no complication to 52 days in a patient with anastomotic leak. Mean duration of hospitalization was 18.8 days. There were no hospital deaths.

Voiding and sexual function

Of 47 patients, two underwent a palliative resection and one had undergone resection of a bladder cancer, and were excluded from the questionnaire study. Three others did not return the preoperative questionnaire. Forty-one completed the preoperative questionnaire. After 6 months, three patients had died: one from myocardial infarction (6 months after operation, aged 80 years), one from a dysfunctioning endocardial valve prosthesis (6 months after operation, aged 73 years) and one from a mesenteric thrombosis (7 months after operation, aged 75 years). For reasons unknown, six other patients did not return the postoperative questionnaires; 32 patients remained evaluable at 6 months. Changed frequency of voiding compared with the situation before operation was experienced by nine of the 32 patients and three patients reported minor bladder control problems, but none was incontinent. Bladder function improved in the postoperative period. After 3 months' follow-up these figures were higher: 17 of 32 reported changed frequency and five of 32 bladder control problems.

Fifteen patients were not sexually active before operation, three were not yet active after operation and the information from one patient could not be used because answers were inconsistent. The mean ages of sexually active and sexually non-active patients were 58 and 70 years respectively ($P = 0.001$). Active and evaluable for sexual function after 6 months were three of 11 women and 19 of 30 men. Dyspareunia after operation was experienced by one woman; the other two noted no difference after operation. In all three women, the SHP was sacrificed during the procedure and the IHP was preserved on both sides. The characteristics of the 19 men are given in Table 2. Preoperative scores of sexual function were compared with postoperative scores for each patient. Two patients were impotent after the operation and three others, who had had no problems before operation, said that after the operation they sometimes had difficulty having an erection.

The effect of different levels of nerve preservation on potency was analysed. Impotence through sacrifice of the SHP only was never observed: all five patients with bilateral preservation of the IHP and sacrifice of the SHP remained potent. Patients in whom there was bilateral preservation of the IHP with or without the SHP (total preservation and bilateral preservation of pelvic plexus with sacrifice of SHP), and those in whom one IHP was partly sacrificed, are compared for erection capacity in Table 3. In the group of patients that underwent the total or bilateral IHP nerve-sparing procedure, only one of 17 was impotent after operation (6 (95 per cent confidence interval 0.1–29) per cent). The erection capacity after unilateral IHP preservation was significantly worse: one of two patients was impotent ($P = 0.037$). Hardness and duration of erection was slightly diminished in six patients. No relationship with level of nerve preservation on these two parameters could be observed. Only three of the sexually active patients underwent APR. No effect of the type of operation (APR or SSP) on sexual function could be determined.

Table 1 Type and frequency of postoperative complications

	No. of complications (n = 47)
Surgical complications	
Wound infection	5 (11)
Abdominal wound dehiscence	1 (2)
Perineal wound dehiscence after APR	5 of 18 (28)
Perineal wound seroma	1 of 18 (6)
Anastomotic leakage after LAR	3 of 28 (11)
Sepsis	3 (6)
Pelvic abscess	1 (2)
Pelvic haematoma	1 (2)
Fistula	1 (2)
Paralytic ileus	5 (11)
Non-surgical complications	
Cardiac	1 (2)
Pneumonia	2 (4)
Other pulmonary	2 (4)
Urinary tract infection	6 (13)
Deep venous thrombosis	1 (2)
Right peroneal nerve palsy	1 (2)

Values in parentheses are percentages. APR, abdominoperineal resection; LAR, low anterior resection

Table 2 Characteristics of 19 sexually active men

Mean(s.d.) (range) age (years)	59(10) (40–73)
Operative procedure	
Sphincter-saving procedure	16
Abdominoperineal resection	3
Astler–Coller classification	
B1	4
B2	5
C2	9
D	1
Pelvic autonomic nerve preservation	
Total*	12
Bilateral IHP†	5
Unilateral IHP‡	2

*Total preservation of autonomic nerves; †superior hypogastric plexus and hypogastric nerve sacrificed, with inferior hypogastric plexus (IHP) preserved on both sides; ‡superior hypogastric plexus and hypogastric nerve sacrificed, with IHP preserved on one side

Table 3 Erection capacity relative to the inferior hypogastric plexus in sexually active men

	Pelvic autonomic nerve preservation	
	Total/bilateral IHP*	Unilateral IHP†
Erection capacity		
Full	14	0
Diminished	2	1
Impotent	1	1

*Total preservation of autonomic nerves or bilateral preservation of inferior hypogastric plexus (IHP); †unilateral preservation of IHP

Table 4 Absence of ejaculation relative to the superior hypogastric plexus in sexually active men with erection ability

	Pelvic autonomic nerve preservation	
	SHP*	No SHP†
Ejaculation		
Yes	10	0
No	1	5

*No structures sacrificed and superior hypogastric plexus (SHP) intact; †SHP and hypogastric nerves sacrificed

Patients who were impotent after the operation obviously could not be evaluated for ejaculation. One patient did not answer the question referring to ejaculation. Of the 16 remaining patients, five patients were permanently unable to ejaculate and one patient often had no ejaculation. The latter were classified as 'no ejaculation due to procedure'. In Table 4, patients in whom the SHP was preserved are compared with those in whom it was sacrificed. Of the six patients unable to ejaculate in five the SHP was sacrificed deliberately during the operative procedure. Of the 11 patients undergoing a total nerve-preserving procedure, only one was unable to ejaculate (9 (95 per cent confidence interval 0.2–41) per cent). However, this patient already had ejaculatory problems before the operation. Ejaculation ability after deliberate sacrifice of the SHP was significantly worse, all patients experiencing dysfunction ($P = 0.003$). One patient experienced a slight improvement in both potency and ejaculation between the third and the sixth month of follow-up. Of the other patients none experienced either worsening or improvement of their sexual function.

Discussion

The mean operating time of 185 min was 50 min longer than the average of 134 min reported for the conventional technique of resection for rectal cancer in the Netherlands⁵. It was, however, well within the range of that reported in other studies. Enker¹² reported 258 min for nerve-preserving surgery and in other reports the operation time varied from 158 to 317 min^{2,13,14}. Mean blood loss was limited to 730 ml. In the Netherlands, an average of 1160 ml in 297 conventional rectal cancer operations was reported⁵. In other reports, blood loss varies with the extent of the resection, from 630 ml for nerve-preserving surgery to 1612 ml for 'conventional' pelvic lymphadenectomy^{2,4,12–14}.

The observed overall postoperative complication rate of 53 per cent (25 of 47 patients) was considerable, but not at variance with other reported values, including 50.1 per cent after rectal surgery¹⁵, 40.2 per cent after low anterior resection¹⁵ and 61 per cent after APR¹⁶. Several studies report overall anastomotic leak rates between 0 and 17.4 per cent^{4,13,15,17}, and the leak rate of 11 per cent (three of 28 patients) in this study is within this range. The incidence of perineal wound dehiscence after APR is rarely documented but has been reported as 6.3 per cent in 158 patients¹³. In contrast, the observed rate in the present study was 28 per cent (five of 18 patients). According to Japanese standards, in the perineal phase of the procedure the skin incision was much wider than is generally performed in the Netherlands and the pelvic floor was widely excised. Only skin and subcutaneous tissues were closed with a thick polypropylene suture. The authors believe that this wide resection is not essential to the operation technique. The rate of 11 per cent (five of 47 patients) for prolonged postoperative paralytic ileus contrasts with an incidence of ileus of 3.5 per cent after conservative rectal resection^{5,13}. Prolonged ileus has been shown to be a common complication of retroperitoneal lymph node dissection in patients with testicular cancer¹⁸. In this series, dissection of lymphatic tissue in the abdominal retroperitoneal space in the first phase of the procedure might explain the high incidence of prolonged paralytic ileus. Fortunately, this always resolved spontaneously. Urinary tract infection rates vary from 11 to 16 per cent and wound infection rates remain high in all reports^{5,13,15}. The mean hospital stay of 19 days was slightly more than that of 17 days reported for conventional surgery for colon and rectal cancer in the Netherlands⁵. In this study there were no postoperative deaths.

Currently, the rate of urinary dysfunction after surgery for rectal cancer ranges from 30 to 70 per cent^{19,20}. This large variation of urinary dysfunction is caused by a wide divergence in patient selection, method of measuring urinary function and time of assessment after surgery. The present results are therefore difficult to compare with existing data. Prospective urodynamic evaluation seems to be the best objective parameter for bladder function²⁰. However, the fact that incontinence as a result of the procedure was not reported by any of the present patients indicates that this complication can be avoided using the operative technique described. The observed improvement of bladder function within the first year after surgery is consistent with the literature^{20,21}.

A high percentage of the patients were not sexually active and therefore could not be evaluated for sexual function. In female patients sexual activity was almost absent, which makes it impossible to draw any conclusions from this study on functional outcome in women. Most studies evaluating sexual dysfunction involve retrospective questioning and rates of sexual activity are not reported. In this study this inactivity appeared to be related to age. However, since the average age of patients diagnosed with rectal cancer is high, the substantial number of patients not sexually active in this study might well be generally applicable to the population of patients with rectal cancer. APR has been identified as an important risk factor for sexual morbidity^{7,22}. Although 18 patients underwent APR, only three could be evaluated. Therefore, the authors cannot confirm nor refute these findings. Results of studies on male sexual function after rectal cancer surgery are shown in Table 5. Impotence varies from 18 to

Table 5 Sexual dysfunction after surgery for rectal cancer

Reference	Year	n	Impotence (%)	Ejaculation disorders* (%)
Kinn and Ohman ⁶	1986	10	33	50
Havenga and Welvaart ⁷	1991	26	34	25
Cunsolo <i>et al.</i> ²³	1990	22	18	59
Santangelo <i>et al.</i> ²²	1987	25	32	24
Danzi <i>et al.</i> ²⁴	1983	25	27	19

*Patients with erections

34 per cent, while 19–59 per cent of potent patients are not able to ejaculate. In a review of the literature, erectile dysfunction occurred in 46 (range 25–100) per cent of 641 men²⁵. The present results concerning sexual function after surgery for rectal cancer are among the best reported; Enker¹² observed impotence in 13 per cent of patients and, of patients with ability of erection, ejaculation was impaired in 12 per cent¹². In the present series, only two (11 per cent) of the 19 men for whom data were available have become impotent. After preservation of the IHP on both sides only one of 17 was impotent after 6 months. Absence of ejaculation after a total nerve-preserving procedure occurred in one of 11 patients. This study indicates a direct relationship between the nerves preserved and the type of dysfunction after surgery. It has been shown in a prospective manner that preservation of the SHP is crucial for ejaculation, and that the IHP is related to erection. That such a relationship could not be established for tumescence and duration of erection may be due to the small number of patients. These results suggest that in the Dutch population the SHP, which in this study was deliberately sacrificed relatively easily, should in the future be sacrificed only when there is evidence for ingrowth of tumour into the plexus. Preservation of the SHP should be possible in a higher percentage of cases than was reached in the population in this study.

In conclusion, the results of this study are promising. However, in interpreting the results, the limits of the design (single cohort) and size ($n = 47$) should be taken into account. This study has shown that applying the principles of nerve-preserving radical resection in Dutch patients did not lead to a significant increase in either mortality or postoperative morbidity rate. The good functional results obtained after surgery with nerve-preserving techniques further strengthen the idea that sexual dysfunction after conventional rectal surgery is the result of damage to specific nervous structures during the operation. Furthermore, the surgeon is considered to be one of the important prognostic factors for tumour recurrence and survival²⁶. Therefore, we believe that standardization of the surgical technique, through education of surgeons in pelvic neuroanatomy and crucial anatomical dissection planes, is the key to major improvement of quality of life and a better chance for cure in patients with rectal cancer.

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Genetic detection of lymph node micrometastases in patients with colorectal cancer

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Background Undetected micrometastases represent the single most important cause of treatment failure in patients undergoing putatively curative resection for colorectal cancer because current staging techniques are unable to identify patients with minimal residual disease.

Methods A highly sensitive reverse transcription–polymerase chain reaction technique has been used to amplify tissue-specific messenger RNA from lymph nodes classified as tumour-free using both conventional histopathology and immunohistochemistry.

Results Four of 15 patients were restaged after genetic diagnosis of lymph node micrometastases, while in a further two additional positive nodes were detected.

Conclusion Sensitive genetic techniques that detect minimal residual disease merit further study, particularly as there is evidence that patients may benefit from adjuvant chemotherapy.

Colorectal cancer accounts for 18 000 deaths every year in the UK with some 25 000 new cases diagnosed each year¹. Adjuvant chemotherapy has an impact on survival² and appropriate patient selection is important. Occult micrometastatic disease represents the single most important cause of treatment failure after a curative operation, accounting for approximately 30 per cent of deaths³. Present staging techniques do not allow the identification of such patients.

A sensitive reverse transcription–polymerase chain reaction (RT-PCR) technique has been employed based on amplification of messenger RNA (mRNA) expressed from the epithelium-specific cytokeratin 20 (CK20) gene. This method has been used to seek micrometastatic cells in patients with otherwise tumour-free lymph nodes.

Patients and methods

Tumours from 18 patients in whom a putatively curative resection for colorectal cancer was performed were included in the study. Operative specimens from a further five patients undergoing large bowel resection for benign disease (confirmed histologically) were also studied. Lymph nodes were harvested from freshly resected specimens and labelled. One-half of each node was kept for conventional histopathology (formalin-fixed and paraffin-embedded), while the other half was snap-frozen in liquid nitrogen for RNA preparation and immunocytochemistry.

RNA preparation

The lymph node tissue was resuspended in lysis buffer (guanidyl thiocyanate 4 mol/l, sodium citrate 0.025 mol/l, pH 7.0, 0.5 per cent Sarkosyl, mercaptoethanol 0.1 mol/l) and homogenized. Total RNA was extracted using a protocol previously described⁴. The RNA was then resuspended in 50 µl of diethyl pyrocarbonate-treated water and quantitated using a GeneQuant RNA/DNA Calculator (Pharmacia Biotech, St Albans, UK).

Polymerase chain reaction and primer sequence

Reverse transcription and PCR were carried out using the EZ one tube–buffer system (Perkin Elmer, Warrington, UK). In each 30 µl reaction, 0.1 µg of total RNA was used. The sense and antisense primers used were those originally described by Burchill *et al.*⁵ to detect the presence of carcinoma cells in peripheral blood. Reverse transcription was carried out for 30 min at 60°C, followed by the amplification step (40 cycles of 94°C for 15 s, 65°C for 45 s). Amplified DNA products were visualized by agarose electrophoresis. All reactions included negative controls, in which the template or the reverse transcriptase were omitted, as well as positive controls of a primary tumour and the human colorectal cancer cell line HT29, both of which express CK20. The RNA quality was assessed by running it on an agarose gel, while viability of the RNA in each lymph node sample was confirmed by amplification of complementary DNA for glyceraldehyde phosphate dehydrogenase (GAPDH).

Cloning and sequencing of polymerase chain reaction products

Bands were excised from agarose gels and sequenced directly on an ABI 370 automated DNA sequencer using the Perkin Elmer sequencing kit. The FASTA program, accessed through the United Kingdom Human Genome Mapping Project, was used to compare the sequences obtained with sequences in the Genbank database.

Southern blot analysis

RT-PCR products were separated on agarose gels and blotted on to nylon membranes (Hybond N; Amersham International, Amersham, UK). Filters were incubated with a ³²P-labelled nucleotide probe (5'-GGCGGCGGGACCTGTTTGTGGC-3') which hybridizes to nucleotide positions 34–57 on the 370 base pair (bp) fragment.

Cell spiking

Cell spiking experiments were performed by adding known numbers of HT29 cells to whole blood. A range of 0–10⁵ HT29 cells was seeded in 10-ml aliquots (containing approximately 10⁷ nucleated cells) of whole blood. Total RNA was extracted and RT-PCR was performed using the above conditions. This revealed that, under the chosen RT-PCR amplification

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parameters, 20 HT29 tumour cells could be detected amongst 10^7 non-tumour cells.

Results

All primary tumours from 18 patients yielded a predicted 370-bp DNA fragment on RT-PCR. Similarly, immunocytochemistry for CK20 revealed strong and homogeneous positivity in all tumours examined. None of the 30 lymph nodes from five patients undergoing colorectal resection for benign pathology (resection rectopexy, one; diverticular disease, two; ulcerative colitis, one; Crohn's disease, one) yielded the 370-bp DNA fragment under the chosen amplification conditions. However, all of these nodes gave a signal for the control GAPDH gene, indicating the extraction of viable RNA. The results of reverse PCR for CK20 in 18 patients with colorectal cancer are shown in Table 1. Conventional histopathology and immunohistochemistry did not reveal any discrepancy in the presence of tumour cells between the two halves of the lymph nodes examined.

In five patients the number of positive lymph nodes was increased by genetic diagnosis using RT-PCR. Three of these patients were restaged, while a further two already had histologically positive nodes. In one patient with a Dukes stage B tumour, a positive CK20 signal was demonstrated on Southern blot analysis in one lymph node although there was insufficient DNA to reveal a 370-bp fragment on gel electrophoresis. Immunocytochemistry for CK20 failed to identify micrometastases in any of the lymph nodes where tumour cells had been detected by RT-PCR or Southern blot analysis. Histopathologically involved nodes also revealed the presence of tumour metastases by genetic diagnosis. In all five cases where occult micrometastases were detected by RT-PCR, the presumed CK20 PCR product was validated by two further investigations. First, a Southern blot of the

amplified DNA was performed using a CK20 DNA probe confirming specific hybridization to CK20. Second, direct sequencing of the PCR DNA also confirmed it as the correct CK20 PCR product. Sequence identities ranging from 96.4 to 99.2 per cent with the human gene for CK20 were obtained, while there were no sequence similarities with other cytokeratin genes.

Discussion

Thirty per cent of patients with no identifiable tumour cells within lymph nodes die from disseminated disease after a putatively curative resection³. Several techniques have been studied in an attempt to increase the detection of occult lymph node micrometastases including methods designed to yield greater numbers of lymph nodes for examination, serial sectioning of lymph nodes and finally immunohistology. These studies are characterized by a lack of agreement as to their prognostic significance⁶⁻¹². The majority have employed immunocytochemistry for cytokeratins to detect lymph node micrometastases, assuming that expression of cytokeratins is an exclusive feature of epithelial cells. However, many other non-epithelial cell types within lymph nodes express cytokeratins, including fibroblasts, lymphoid and endothelial cells¹³.

CK20 is a recently identified polypeptide whose expression is largely restricted to gastric and intestinal epithelium¹⁴. Unlike other cytokeratins used to detect micrometastases, this transcript is not present in endothelial and lymphoid cells or other cell types normally found in lymph nodes. It is expressed in almost all colorectal cancers¹⁵ and this expression remains stable in lymph node metastases.

Molecular biology techniques allow the detection of molecular markers present at low copy numbers with a sensitivity significantly greater than that achieved by immunocytochemistry¹⁶. PCR has been used to detect both lymph node micrometastases¹⁷⁻²¹ and circulating tumour cells^{5,22} in a number of different malignancies. These techniques either employ the amplification of tumour-specific, and therefore mutated, DNA sequences²⁰ or are based on the detection of mRNA expressed selectively by the tumour cells (RT-PCR)^{5,17-19,21,22}. As there are no known mutations that occur consistently in all colorectal cancers²³, DNA-based techniques are restricted to tumours harbouring the specific mutations under investigation. RNA-dependent techniques, on the other hand, can detect expression of wild-type mRNA without the presence of mutations. Any tumour cells detected are highly likely to be viable because of the extremely labile nature of mRNA. This observation may be important in determining the biological significance of such cells in relation to subsequent patient outcome.

Results from this small study have led to the genetic restaging of four patients and detected additional lymph node metastases in two patients with Dukes C tumours. This technique is more sensitive than histopathology or immunocytochemistry and could identify micrometastatic (CK20-positive) epithelial cells within lymph nodes. Presently, no recurrent or metastatic disease has been detected in the four patients who were restaged in this study (follow-up 1-13 months).

Using a mutant allele-specific amplification technique, Hayashi *et al.*²⁴ have demonstrated that genetic detection of lymph node metastasis is a useful prognostic indicator

Table 1 Genetic diagnosis of lymph node metastases by detection of CK20 RNA

Sex	Age (years)	Dukes stage	Site	Conventional histopathology	RT-PCR for CK20
M	38	B	Caecum	0 of 5	1 of 5*
F	71	C	Caecum	12 of 18	12 of 18
F	73	B	Sigmoid	0 of 8	0 of 8
F	84	B	Rectum	0 of 6	0 of 6
M	69	B	Rectum	0 of 5	1 of 5*
M	73	B	Rectum	0 of 8	0 of 8
M	67	B	Caecum	0 of 8	0 of 8
M	86	B	Rectum	0 of 8	0 of 8
M	42	B	Rectum	0 of 6	0 of 6
F	70	B	Rectum	0 of 16	1 of 16‡
F	77	B	Rectum	0 of 9	0 of 9
M	82	B	Rectum	0 of 11	0 of 11
F	76	B	Hepatic flexure	0 of 6	2 of 6*
F	62	B	Sigmoid	0 of 10	0 of 10
F	65	B	Rectum	0 of 8	0 of 8
M	79	C	Caecum	15 of 15	15 of 15
M	55	C	Rectum	8 of 11	9 of 11†
F	66	C	Sigmoid	3 of 7	5 of 7†

*Patients restaged by genetic diagnosis of lymph node metastases; †patients in whom additional lymph node metastases were diagnosed; ‡patient in whom nodal metastasis was diagnosed by Southern blot. RT-PCR, reverse transcription-polymerase chain reaction

in patients with colorectal cancer. RT-PCR has been employed previously to detect micrometastatic tumour cell mRNA in the lymph nodes of patients with colorectal cancer^{21,25}. The target mRNA sequences used in these studies (carcinoembryonic antigen (CEA)²¹ and CD44²⁵) are problematic. For instance, there is considerable variation in the level of CEA mRNA expressed by colorectal cancer cells²⁶. The lymphocyte homing receptor CD44 has numerous splice variants and not all carcinomas express the variant containing exon v6 which confers metastatic potential²⁷. In particular, CD44v6 expression is absent altogether from some metastatic colorectal cancers²⁸. These pitfalls are obviated by the use of CK20 which is constitutively expressed at high levels in colorectal cancers and their metastases¹⁵.

The present RNA-based technique identifies viable micrometastatic cells. The biological significance of this finding will become clear only with extended patient follow-up in larger studies as 30 per cent of patients with histopathologically proven lymph node metastases do achieve long-term survival. Given the relative inaccuracy of predicting treatment failure after resection of Dukes B colorectal cancer, or, indeed, cure after surgery for Dukes C tumours, such techniques merit further study.

Acknowledgements

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International differences in survival from colon cancer: more effective care *versus* less complete cancer registration

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Background Reporting of a recent international comparison of cancer survival rates has left an impression of inadequate treatment of patients in the UK but failed to address adequately the extent to which differences in survival may reflect variation in the completeness and accuracy of cancer registration. The aim of this study was to quantify the extent to which differences in registration practice may confound comparisons of survival from cancer of the colon.

Methods A cohort of incident cases of colon cancer identified from records held by the North Western Regional Cancer Registry was used to simulate the effects on survival of changes in clinical and registration factors. The survival curve produced after each simulation was compared with that for aggregated data from 21 European registries.

Results The observed survival differences were not explained by more effective primary treatment or by misclassification of *in situ* cases as malignant disease, whereas the exclusion of cases with only a clinical diagnosis produced estimates close to those of the European cohort.

Conclusion The observed survival differentials may not be due to differences in the quality of care but may reflect the failure of some European registries to register all patients with advanced disease.

An estimate of survival following a diagnosis of cancer is a commonly used measure of the effectiveness of patient care; that which describes the outcome in an entire population is particularly useful because the totality of this experience cannot be inferred from clinical series. Popular reporting of a recent comparison of cancer survival rates, based on cancer surveillance data collected by national and regional cancer registries in 11 European countries¹, has left an impression of inadequate treatment of patients in the UK. Before drawing such a conclusion, it would be wise to attempt to quantify the extent to which differences in data quality, data handling and registration practice may confound comparisons of survival.

Cancer registry surveillance data are subject to three sources of error: incomplete ascertainment of cases, incomplete notification of deaths and misclassification, either random or systematic. Another influential element will be 'local practice' in registration procedures. The possible impact on survival estimates of these factors is now considered.

It is not widely appreciated that some patients with cancer will have minimal contact with inpatient hospital services². For some patients with advanced disease no attempt will be made to obtain histological confirmation of disease and for others the death certificate may be the only notification of a cancer to the registry. The former are registered on the basis of a clinical diagnosis and are included in survival analyses; the latter are registered as death certificate only (DCO) registrations and by convention are excluded. A diligent and well resourced registry will attempt to minimize its DCO registration rate by actively seeking details of the previous medical history for such patients. Other registries, which are solely dependent on inpatient hospital records, or are not provided routinely with death notifications or lack the

resources to seek supporting clinicopathological evidence, will exclude from analyses relatively more of these patients, many of whom are poor survivors.

Some registries use active follow-up procedures to ascertain death, while others depend on passive measures. Active follow-up involves contacting either the hospital or general practitioner responsible for the patient's care on a regular basis, to confirm vital status. In England and Wales cancer registration operates at the regional level but is coordinated nationally through the Office for National Statistics and the National Health Service Central Register. This approach allows, first, for registries to receive death certificates with any mention of cancer notified in the region and, second, for automatic notification of death, from whatever cause, for registered cases. This passive system is more efficient than that operating in countries where linkage of records is difficult because of privacy regulations³. Estimates of survival must be assumed to be inflated for countries without ready access to death certificates³.

Some cancer sites have a common and well defined premalignant stage which, if systematically confused with invasive carcinoma either diagnostically or during the subsequent abstraction and encoding of information, would lead to inflated estimates of survival. Misclassification may also occur when there is no opportunity to obtain histological confirmation of disease. Such cases will include a relatively high proportion of elderly debilitated patients with advanced disease who are considered poor operative risks. The clinical diagnosis of the abdominal tumour in these circumstances might be recorded as 'colon cancer' by some clinicians, or as 'cancer of the large bowel' or even as 'unknown primary' by others. Local practice in the coding of non-specific sites may also vary. For instance, although the International Classification of Diseases (ICD)⁴ allows for a diagnosis of 'large bowel, not otherwise specified' to be included under rubric 153 (colon cancer), if the diagnosis is based on a tentative clinical opinion, it may be coded to other

rubrics. Again, such tumours are likely to be of poor prognosis and their exclusion from an analysis of 'colon' cases would inflate survival for this site.

Anniversary date is the index date from which the period of survival is measured. Unfortunately, it is defined in many different ways: 'date first seen for the condition by any medical practitioner', 'date first seen in hospital', 'date first treated', 'date of diagnosis' or 'date of first pathology report'. Such different usages affect the measurement of survival merely by shifting the starting point, giving rise to a lead-time bias. A similar effect may occur when screening or early diagnosis advances the date of diagnosis without postponing the date of death.

Further difficulties arise in estimating survival from population-based data: first, it is not always possible to decide whether a death is due to cancer or from unrelated causes and, second, both cancers and deaths from other causes are more frequent in older people. To overcome these problems it is usual to include all deaths in the analysis but to allow for other causes of death by calculating the relative survival rate², defined as the ratio of the crude rate to that which would be expected as a result of the deaths in an underlying population similarly constituted with respect to age and sex.

The effects of five potential confounding factors on estimates of survival – DCO registrations, clinical diagnoses, large bowel not otherwise specified, misclassification and lead-time bias – have been investigated and contrasted with the effect of varying the cure rate. As an illustrative example the relative survival of patients with colon cancer registered with the North Western Regional Cancer Registry (NWRCR) is compared with that reported from the European Cancer Registry-based Study of Survival and Care of Cancer Patients (EUROCARE) project³.

Patients and methods

All incident cases of colon cancer (ICD9 153) registered with the NWRCR with an anniversary date between 1985 and 1989 were identified. A potential 5-year follow-up was available for every case.

Conventional relative survival analyses were carried out, using a widely accepted computer package⁴, to produce a survival curve for the North West cohort, after removal of the observed DCO registrations. This was compared with the estimate derived from the aggregated data published by the EUROCARE project for the years 1984–1985.

The composition of the North West cohort was modified to explore the individual effects on estimates of relative survival of increasing DCO rates, lead times of different duration, different rates of misclassification of *in situ* disease, reducing the proportion of clinically diagnosed cases and more effective treatment. This was achieved by repeating the analyses after the removal of specified subsets of cases, the addition of dummy cases or changing the outcome for selected cases. All clinically diagnosed cases and those registered as 'large bowel, not otherwise specified' were in turn removed from the cohort. By first including the DCO cases in the analysis and then excluding them, the expected probability of survival attached to DCO cases could be ascertained and used to assess the effect of doubling the DCO rate.

Lead time was introduced into the data by advancing the anniversary date for each member of the cohort by 3, 6 and 9 months in succession. An increase in the numbers of misclassified cases was effected by duplicating every 20th, tenth and fifth case, which had been verified histologically and by assuming that these duplicates survived their 'cancer' but were still subject to death from other causes. It is also possible that

the differences could result from more effective therapy. To simulate the effect of an increasing cure rate, therefore, increasing proportions of patients with a histological diagnosis who had died were deemed to have survived their cancer, but still to be subject to death from other causes.

The survival rate for the first year's follow-up is presented separately from the remainder of the curve, which describes the survival for the 1–5 year period for those patients who survived the first year following diagnosis.

Results

Estimates of relative survival are summarized in Table 1 for three follow-up intervals: year 1, years 1–5 and the overall 5-year period, measured from anniversary date. Baseline rates for the North West cohort ($n = 6457$) were 55, 68 and 38 per cent for the three follow-up intervals respectively, and the corresponding figures for the EUROCARE cohort ($n = 15000$ approximately) were 64, 70 and 45 per cent. Estimates resulting from the various modifications to the North West cohort are also included in the Table. Doubling the DCO rate only improved the 5-year survival by 3 per cent. Introducing a lead time of 6 months more than compensated for the first year deficit but survival in the first year is offset by a lower rate in the later years, because the date of death is not affected, only shifted backwards in the time scale. The exclusion of cases coded to 'large bowel, not otherwise specified' also had little effect.

Modifications which came closest to reproducing the EUROCARE 5-year survival rate (45 per cent) were an increase of 10 per cent in the cure rate, a 20 per cent rate of misclassification of *in situ* cases as invasive disease, and

Table 1 Cumulative relative survival rates (%) for three follow-up intervals, for the EUROCARE cohort and the North West cohort before and after modification to simulate the effect of changes in clinical and registration factors

	Effective sample size (0–5 years)*	Follow-up interval (years)		
		0–1	1–5	0–5
North West cohort	5965†	55 (54–56)	68 (66–71)	38 (36–39)
Exclusions				
Double DCOs	5473	60	68	41
Large bowel NOS	3872	58	67	39
Clinical diagnoses	4552	66	68	45
Lead time				
+ 3 months	5965	60	64	39
+ 6 months	5965	67	55	37
<i>In situ</i> disease				
+ 5%	6192	57	70	40
+ 10%	6421	58	72	42
+ 20%	6875	61	76	46
Cure rate				
+ 5%	5965	57	74	41
+ 10%	5965	60	77	46
+ 20%	5965	64	84	54
EUROCARE cohort	15000 approx	64	70	45

Values in parentheses are 95 per cent confidence intervals. *Number of subjects whose complete follow-up would produce a standard error equal to that observed for the cumulative survival estimate at 5 years. †Excluding death certificate only (DCO) registrations; NOS, not otherwise specified

the exclusion of all clinically diagnosed cases. However, inspection of the divided curves shows that although increasing the number of *in situ* cases (Fig. 1a) or the proportion of cured cases (Fig. 1b) improved the 1-year survival rate, they also resulted in survival estimates for the 1–5 year period substantially in excess of those for the EUROCORE cohort. Estimates based on the exclusion of cases with only a clinical diagnosis, came closest to

reproducing those for the EUROCORE cohort in each follow-up interval (Fig. 1c).

Discussion

This analysis suggests three possible explanations for the 5-year survival advantage enjoyed by the EUROCORE cohort: more patients may have been 'cured', a larger proportion of patients with *in situ* disease may have been misclassified as having invasive disease or a substantial number of cases of advanced disease were not ascertained. More patients might be 'cured' if primary treatment were more effective as a result of either earlier diagnosis resulting in a more favourable stage distribution, or greater technical competence or the more widespread use of adjuvant chemotherapy, although the latter is unlikely for this period. More effective primary treatment will reduce the proportion of patients presenting with recurrent or disseminated disease. As most patients who die from these sequelae do so in the later years of follow-up, more effective primary treatment should result in greater improvement in survival in years 1–5 than in the first year, a prediction confirmed by the simulation (Fig. 1c). However, the difference in survival between the two cohorts was less for years 1–5 (2 per cent) than in the first year (9 per cent), suggesting that differences in treatment are unlikely to explain the observed survival differential.

Including an additional 20 per cent of *in situ* cases in the North West cohort would reproduce the 5-year survival of the EUROCORE cohort but not simulate the pattern of survival in the preceding individual years. Misclassification on this scale does not appear plausible.

However, failure to ascertain every case with advanced disease is a credible explanation because the exclusion of patients with clinical diagnoses from the North West cohort produced a survival curve very similar to that of the EUROCORE cohort. For countries in the EUROCORE cohort, Sant *et al.*³ reported a significant correlation (Pearson's $r = 0.9$) between survival rates and the proportion of cases for which histological confirmation of colon cancer had been obtained. This, they inferred, was indicative of a higher proportion of cases presenting with late-stage disease in countries with a low survival rate. That the result was also consistent with under-ascertainment of late-stage disease in countries with a high survival rate was not mentioned as a possibility.

The results of this study suggest that the latter is the more likely explanation. If both cohorts had ascertained every case, but as a result of a less favourable stage distribution in the North West cohort fewer patients were cured, then it might have been expected that the survival differential would have been abolished by increasing the cure rate for the North West cohort. The simulation model suggests that this is not the case (Fig. 1b). Alternatively, if ascertainment is incomplete for the EUROCORE cohort, because of failure to ascertain all clinically diagnosed cases, then only removal of these cases from the North West cohort is likely to produce comparable populations. The simulation exercise suggests that when this is done, the survival of the two cohorts is similar (Fig. 1c).

Cancer registries aim to collect information on all cases of cancer occurring in a defined population. Efficient registration depends on developing systems for collecting and collating data from diverse sources in order to attain high levels of registration, in terms of both quality and

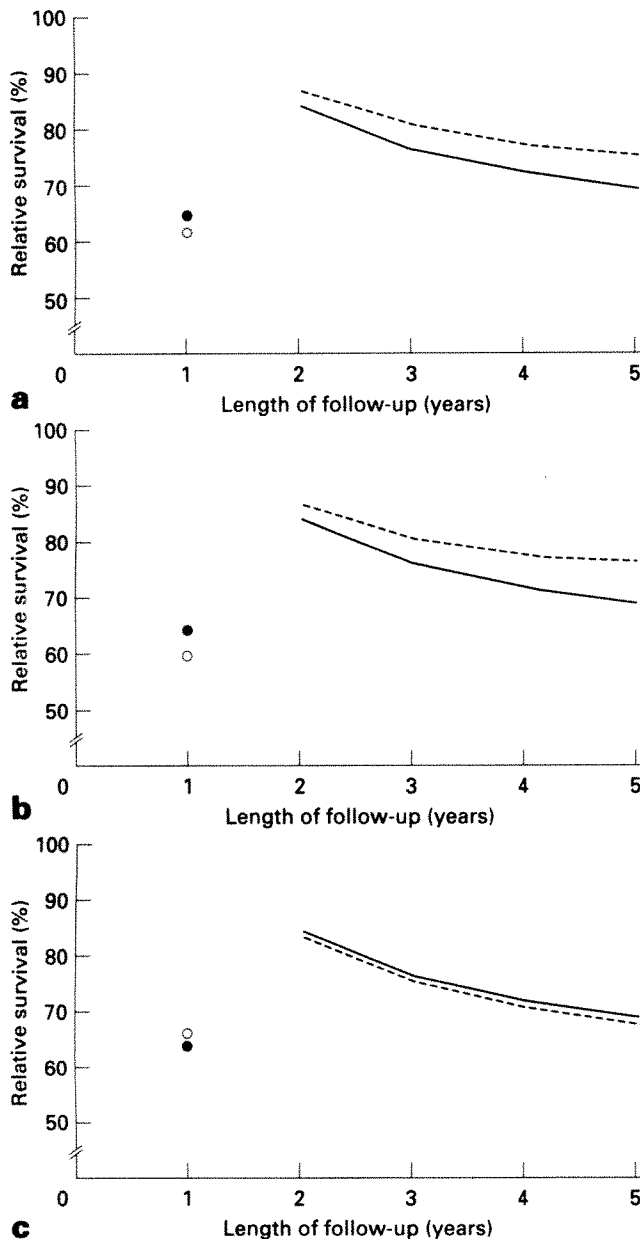


Fig. 1 Cumulative relative survival for the EUROCORE cohort (—, ●) and the North West cohort (---, ○) after modification by a increasing the number of histologically verified cases by 20 per cent by the addition of *in situ* cases misclassified as malignant, b curing 10 per cent of the histologically verified cases who had died and c excluding all cases with a clinical diagnosis only. Survival for year 0–1 is presented separately from that for the 1–5-year period for those patients who survived the first year following diagnosis

quantity. Reliable, population-based estimates of survival are dependent on access and efficient linkage to death notifications. Comparisons across populations which vary in accuracy and completeness of registration can be misleading and should be treated with some circumspection. It is probable that no single factor can satisfactorily explain the difference between North West estimates and those of individual countries but it would seem that the longer established registries can demonstrate more complete coverage for their populations. Differences in outcome may, therefore, not reflect differences in quality of care but more effective cancer registration.

It is not suggested that there should be complacency about survival rates for colon cancer in the UK. The population-based results of this study emphasize, first, that the impressive outcomes reported from some hospital series are not achieved in the population as a whole and, second, that substantial improvements in survival are most

likely to follow from a reduction in the number of patients presenting with advanced disease.

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Marsupialization of fistulotomy wounds improves healing: a randomized controlled trial

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Background Marsupialization of anal fistulotomy wounds leaves less raw unepithelialized tissue to granulate and may improve wound healing.

Methods Some 103 consecutive patients with uncomplicated intersphincteric or trans-sphincteric fistula *in ano* were recruited into a randomized controlled trial. Fistula tracts were identified and laid open under general anaesthesia. The patients were randomized to have either the wounds left open (LO group) or wound edges marsupialized to the fistula tract with interrupted absorbable sutures (MS group). Anal manometry was performed before operation, and 6 weeks and 3 months after surgery.

Results Some 52 patients were randomized to the LO group and 51 to the MS group. There were no differences in the age, sex, fistula type and fistula length distribution between the groups. Mean follow-up times were 9 and 10.2 months respectively. Wounds in the MS group healed faster (mean(s.e.m.) 6.0 (0.4) weeks) than those in the LO group (10.0 (0.5) weeks) ($P < 0.001$). Only one patient (2 per cent) in the MS group was incontinent of liquids after operation compared with six (12 per cent) in the LO group. There was less impairment in maximum anal squeeze pressure at 3 months after marsupialization compared with leaving fistulotomy wounds open ($P < 0.05$). Apart from a slightly longer operative time required for marsupialization, the hospitalization and complication rates were the same.

Conclusion Anal fistulotomy wounds healed faster after marsupialization. Anal squeeze pressures were better preserved and this may improve anal continence.

Anal fistulas may be cured by fistulotomy but this may involve prolonged wound healing and compromise of anal continence¹. The laid open fistula tract may be marsupialized to the wound edges leaving less raw unepithelialized tissue to heal over^{2,3}. This may result in more rapid wound healing and less deformity compared with leaving the wound open. However, marsupialization is not widely accepted because there are inadequate randomized controlled data comparing fistulotomy with or without marsupialization. The present study compared the clinical and anal manometric outcome of these two techniques.

Patients and methods

One hundred and three consecutive patients with fistula *in ano* were recruited with informed consent. Complex fistulas with multiple openings, horse-shoe tracts, suprasphincteric and extrasphincteric fistulas, as well as recurrent fistulas were excluded. All patients were fully continent of gas, liquid and solid stools. Randomization was by drawing sealed envelopes. Surgery was performed under general anaesthesia in the lithotomy position. The radial distance of the external opening to the anal verge was measured. The fistula tract was examined by palpation and proctoscopy. A Lockhart-Mummery probe was inserted and the tract was laid open. Secondary tracts were carefully excluded. The granulation tissue lining the tract was curetted out.

In patients randomized to the LO group, a minimal amount of perianal skin on each side of the incised tract was excised to form a small ellipse. This was designed to prevent premature skin healing, before granulation from the depths of the wound was completed. The fistulotomy wounds were gently packed with

saline gauze for 24 h. In the MS group, marsupialization of the wound was performed (Fig. 1). The anoderm and skin at the wound edges were sutured to the sides of the laid open fistula tract^{2,3} with interrupted polyglactin. Patients in both groups were given routine postoperative analgesia, fibre supplements, oral analgesics and sitzbaths. On discharge from hospital, they were continued on the sitzbaths until complete healing took place. Outpatient review was on a weekly basis until the wounds healed, and then at 3-month intervals. The patients were questioned specifically on their faecal continence during each visit.

Anal manometry was performed using a microcapillary perfusion system (Synectics, Stockholm, Sweden)^{4,5}. The procedure was performed before operation, and at 6 weeks and 3 months after surgery.



Fig. 1 Marsupialization of fistulotomy wound. The skin edges on each side of the wound were sutured to the sides of the laid open fistula tract with interrupted stitches

Data are expressed as mean(s.e.m.). Statistical significance was tested using the Mann-Whitney non-parametric test and χ^2 test where appropriate.

Results

Fifty-two patients were randomized to the LO group, of whom 49 were men and three women, with a mean age of 41.1(1.9) years. Twenty-seven (52 per cent) of them had intersphincteric and 25 (48 per cent) had trans-sphincteric fistulas. The mean radial distance of the external opening from the anal verge was 5.2(1.0) cm. Mean follow-up in this group was 9(0.4) months. Fifty-one patients in the MS group comprised 41 men and ten women, with a mean age of 41.2(1.6) years. Twenty-seven (53 per cent) of them had intersphincteric and 24 (47 per cent) had trans-sphincteric fistulas. The mean radial distance of the external opening from the anal verge was 5.9(1.5) cm. Mean follow-up in this group was 10.2(0.5) months. There were no significant differences in the age, sex, type of fistula, radial distance of the external opening from the anal verge and follow-up period between the two groups. Marsupialization of the wound added slightly to the operative time (10(0.7) versus 8.0(0.5) min for LO group; $P < 0.05$). The postoperative hospital stay was similar between the two groups (LO 2.0(0.2) days; MS 1.0(0.1) days).

Clinical outcome

Marsupialization of the wound resulted in significantly faster healing (6.0(0.4) versus 10.0(0.5) weeks for LO group; $P < 0.001$). This took into account two marsupialized wounds (4 per cent) which broke down. At follow-up, only one (2 per cent) of patients in the MS group complained of incontinence (to liquid stools and flatus) compared with six (12 per cent) in the LO group. However, this difference did not reach statistical significance. The patient in the MS group and three of the six whose wounds were left open recovered full continence on expectant treatment, at the end of the follow-up period. The fistula recurrence rates (LO two (4

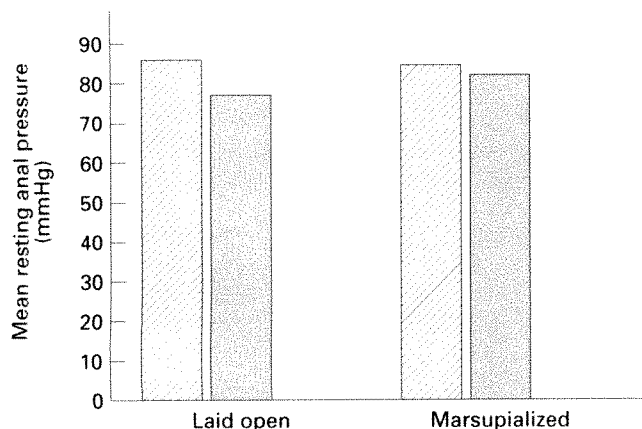


Fig. 2 Mean resting anal pressures before (▨), and 6 weeks (▤) and 3 months (□) after surgery comparing laying open and marsupialization of fistulotomy wounds. Values are mean (s.e.m.). There were no differences in the mean resting anal pressure changes at 6 weeks and 3 months after either procedure (Mann-Whitney U test).

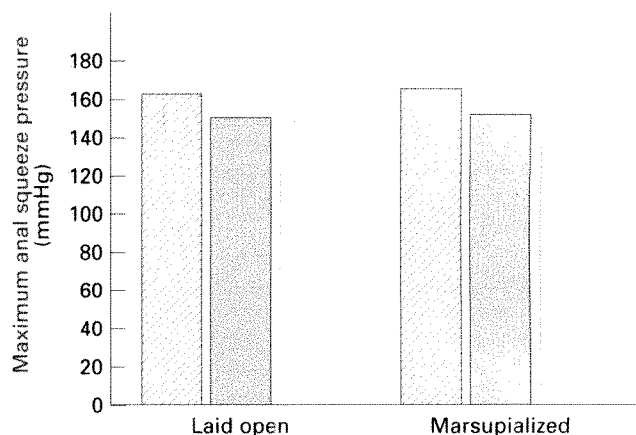


Fig. 3 Mean(s.e.m.) maximum anal squeeze pressures before (▨), and 6 weeks (▤) and 3 months (□) after surgery, comparing laying open and marsupialization of fistulotomy wounds. The drop in anal pressure at 3 months was significantly greater after laying open than marsupialization ($P < 0.05$; Mann-Whitney U test). There was no difference in these pressure changes at 6 weeks.

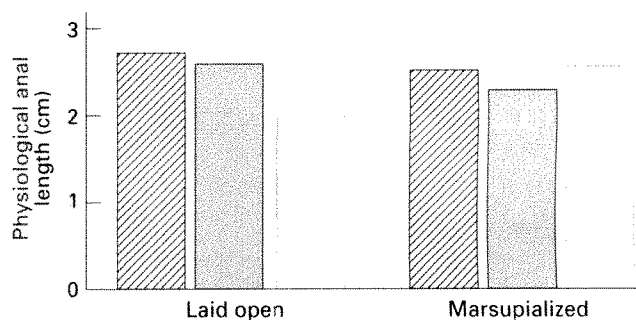


Fig. 4 Mean(s.e.m.) physiological anal length before (▨), and 6 weeks (▤) and 3 months (□) after surgery, comparing laying open and marsupialization of fistulotomy wounds. There was no difference in the anal length change at 6 weeks and 3 months after either procedure (Mann-Whitney U test).

per cent); MS one (2 per cent)) were no different. No other complications were encountered in either group.

Anal manometry

The preoperative and postoperative mean anal resting pressures (Fig. 2), maximum anal squeeze pressures (Fig. 3), and physiological anal length (Fig. 4) are shown. There was a significantly greater drop in the maximum anal squeeze pressure at 3 months in the LO group compared with the MS group (Fig. 3; $P < 0.05$).

Discussion

It was found that marsupialization of fistulotomy wounds resulted in more rapid healing. This might be expected from the smaller surface left open to granulate. The extent and length of the fistula tracts were similar in the MS and LO groups. A small number (4 per cent) of

marsupialized wounds broke down, but all these healed uneventfully afterwards. Rapid wound healing rates after marsupialization were comparable to an average of 3.5 weeks quoted in a previous smaller retrospective uncontrolled study². It was also found that marsupialization better preserved the maximum anal squeeze pressure at 3 months after fistulotomy. This is consistent with suggestions that the deformity and scarring of the external anal sphincters is less after marsupialization of the wound². Clinically, one patient (2 per cent) in the MS group developed temporary incontinence to liquids and gas compared with six (12 per cent) in the LO group, of whom three had not recovered at the end of follow-up. It was possible that statistical significance could have been attained with more patients. The 2–12 per cent incidence of clinical incontinence after fistulotomy was comparable to the values of 3–11 per cent reported previously^{6–8}.

Marsupialization of the wound lengthened the operative time (by a mean of 2 min) but incurred no other disadvantages. The hospitalization time and postoperative complication rate were the same. The recurrence rates of 2 per cent in the MS group and 4 per cent in the LO group were consistent with previous reports of 2–8 per cent^{1,6,9–11}, although the follow-up period in the present study was relatively brief. None the less, the data suggest that marsupialization of laid open uncomplicated intersphincteric and trans-sphincteric fistula tracts results in more rapid and less deformed wound healing.

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Flap advancement and core fistulectomy for complex rectal fistula

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Background The treatment of low fistula *in ano* is well accepted but controversy surrounds the management of high trans-sphincteric fistulas and more complex fistulas. This study assesses the clinical results of advancement flap techniques in association with core fistulectomy for complex fistula *in ano*.

Methods A retrospective analysis of the use of advancement flap techniques together with core fistulectomy in 25 patients (26 fistulas) was performed. Clinical outcome was assessed in terms of fistula healing, continence, failure and technical problems.

Results Successful healing of 20 of the 26 complex fistulas was achieved using this technique with no disturbance of continence and minimal (technical) complications.

Conclusion Flap advancement and core fistulectomy is a safe, effective procedure for complex rectal fistulas with good functional results and minimal or no disturbance of continence, and should be considered for the treatment of complex perianal fistulas.

Fistula *in ano* is a common condition associated with appreciable inconvenience and morbidity to the patient. Conventional classification and treatment depends on the level of the internal opening and the extent of involvement of the external sphincter encompassed by the fistulous track. Simple low fistula (low trans-sphincteric and intersphincteric) may be treated by simple fistulotomy with minimal risk to faecal continence. High fistulas (high trans-sphincteric or suprasphincteric) have been treated by a number of techniques (fistulotomy, rerouting fistula tracks, loose and tight seton sutures) with variable results in terms of recurrent fistula and disturbance of continence^{1–3}. More recently the so-called mucosal flap advancement has been suggested as an alternative technique for the treatment of high fistulas^{4,5}.

The use of advancement flap techniques in a heterogeneous group of patients with complex fistulas is reported, and the surgical technique and clinical results are discussed.

Patients and methods

Between 1 January 1987 and 31 July 1995, 25 patients with complex rectal or neorectal fistulas were referred. Eighteen patients (nine men) had documented idiopathic high trans-sphincteric fistula *in ano* classified according to the method of Parks *et al.*⁶ (fistula track passing deep to more than 50 per cent of the external sphincter muscle), four patients had obstetric rectovaginal fistulas and three patients had pouch–vaginal fistulas (two following pelvic ileal pouch construction after restorative proctocolectomy for ulcerative colitis; one following colopouch construction after low anterior resection for constipation). Mean age of the patients was 38 years (men 42 years; women 37 years).

Previous treatment

All patients had undergone previous operative treatment. Six patients had previously had the bowel defunctioned (three ileostomy, three colostomy) without resolution of the fistula.

Thirteen had been treated previously by loose seton sutures (two patients twice), 23 drainage procedures had been carried out in 15 patients and three patients had undergone attempted surgical closure of a rectovaginal fistula (one patient undergoing two repair attempts before flap advancement).

Surgical technique

In all patients acute perianal sepsis was allowed to resolve before consideration of flap advancement and all patients underwent careful examination in the conscious state and under anaesthetic to delineate fistula anatomy and the relationship to the anal sphincter before surgery. Endoanal ultrasonography and magnetic resonance imaging were used as an adjunct to clinical examination when an underlying sphincter defect or complex secondary tracks were suspected clinically. No patient had clinical or biopsy evidence of Crohn's disease.

Patients underwent mechanical bowel preparation before operation. Patients were positioned in the lithotomy or prone jack-knife position depending on the location of the fistula. Prophylactic antibiotics were administered to all patients.

For idiopathic fistula *in ano*, the standard practice was to perform core fistulectomy in addition to rectal flap advancement, by dissecting out the primary track (and any secondary tracks where possible) using sharp dissection and traversing the external sphincter until the internal sphincter was exposed. The track was then transected. In this series, 16 of the 18 patients underwent fistulectomy in addition to flap advancement.

The technique used for flap advancement (either rectal ($n = 21$) or vaginal ($n = 5$)) has been described previously⁷. After operation, antibiotics were continued until the rectal pack was removed. The patient was allowed to drink freely for 5 days followed by normal diet and bulk laxatives. The external fistulectomy wound was dressed daily.

No patient who had not previously had the bowel defunctioned required a defunctioning stoma to cover the flap advancement procedure.

The technique was essentially the same in the treatment of rectovaginal or pouch vaginal fistulas with a proximally based flap on either the 'rectal' or vaginal aspect of the fistula advanced to cover the defect.

Follow-up included symptom assessment, direct questioning and clinical assessment. Recurrence was defined as a discharge or abscess arising in the same area, or by obvious evidence of fistulation.

Results

Of 26 flap advancement procedures, 20 were successful (17 of 21 rectal; three of five vaginal) with no evidence of

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recurrence of the fistula after mean follow-up of 14 (range 3–60) months. There was no complaint of faecal incontinence following surgery although one patient with successful resolution of a pouch–vaginal fistula declined closure of a defunctioning ileostomy.

The procedure failed on six occasions in five patients; there were three failures in patients with idiopathic fistula *in ano*, one failed vaginal flap for colopouch–vaginal fistula, one failed rectal flap and a failed vaginal flap in the same patient with obstetric rectovaginal fistula (subsequently healed after perineal interposition). Minor technical problems (flap haematoma, two; flap tip breakdown, one) occurred in three rectal flap advancements but did not result in fistula recurrence. One 56-year-old man developed postoperative urinary retention requiring urinary catheterization for 72 h. Spontaneous voiding was achieved following removal of the catheter.

Discussion

The management of low trans-sphincteric and intersphincteric fistulas by laying open of the track and drainage of the intersphincteric space achieves the aims of fistula surgery without compromising continence. This technique, if applied to high fistulas, risks continence by division of an otherwise healthy external anal sphincter and often results in perianal scarring which may further compromise functional outcome^{8,9}.

Noble¹⁰ originally described the rectal flap advancement in 1902, using a full thickness rectal wall flap in the repair of a rectovaginal fistula. This technique was applied to idiopathic fistula *in ano* by Elting in 1912¹¹ and subsequently modified by Laird, who described a partial thickness rectal wall flap¹². Essentially this technique has been adopted by most authors with minor modification and most agree that it should be performed after any acute sepsis has settled.

Aguilar and colleagues¹³ have reported good results using this technique in a heterogeneous group of patients with fistula *in ano* although the exact relationship of the fistula to the external sphincter musculature was unclear in their report. Wedell *et al.*¹⁴ reported a series of 27 patients with trans-sphincteric or suprasphincteric fistula treated in this fashion, achieving closure in 26 of 27 cases. An overview of flap advancement has been reported by Kodner and colleagues¹⁵, outlining an initial success rate of 84 per cent and a secondary success rate of 94 per cent following further surgery (including four further attempts at flap advancement). The flap advancement technique appears less successful for closure of Crohn's fistulas¹⁶.

In this series, successful closure of idiopathic high trans-sphincteric fistula was achieved by primary procedure in 15 of 18 cases. Rectovaginal fistulas were successfully closed in three of five cases and two of three pouch–vaginal fistulas were treated successfully by vaginal flap advancement, a technically easier procedure than rectal flap advancement after a pouch–anal anastomosis. Overall the success rate was 20 of 26. None of these patients had a fistula associated with Crohn's disease.

Failure occurred following six flap advancements in five patients and was likely to be due to infection arising beneath the flap, possibly because of secondary infection of a flap haematoma. Ischaemia of the flap is theoretically an early problem, although this was observed in one case only resulting in flap tip breakdown but no recurrence of

the fistula after revisional surgery.

The effect of fistula surgery on continence is difficult to assess but reports in the literature suggest that the application of a cutting/tight seton suture is associated with minor incontinence in up to 50 per cent and major incontinence in 10 per cent². Even simple fistulotomy for low fistula has been associated with 34 per cent disturbance of continence⁹.

The effect of flap advancement techniques on faecal continence has been reported to be low with up to 10 per cent minor incontinence in one report¹³ and a low incidence of disturbed continence in another study¹⁷. In the present series, no incontinence was reported following fistula repair using this technique. In a previous preliminary report using this technique⁷, 11 patients underwent anorectal physiological assessment before and after operation with no significant difference demonstrated in rest or squeeze pressures or anal canal sensation when comparing preoperative and postoperative physiological data.

In conclusion, flap advancement and core fistulectomy is a safe, effective procedure for complex rectal fistula with good functional results and minimal or no disturbance of continence, and should be considered for the management of complex perianal fistula.

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Surgical workshop

Gastric access loop in hepaticojejunostomy

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Hepaticojejunostomy for benign bile duct stricture is associated with stricture rates of 10–30 per cent with time¹. Many access loops have been designed to facilitate non-surgical intervention for this complication of hepaticojejunostomy^{2–4}. This paper describes a procedure modified from that of Stiegmann *et al.*⁵ which incorporates a jejunogastrostomy and provides the added advantage of easier endoscopic access.

Surgical technique

The end of the Roux-en-Y loop taken up for hepaticojejunostomy is not closed but is anastomosed to the anterior wall

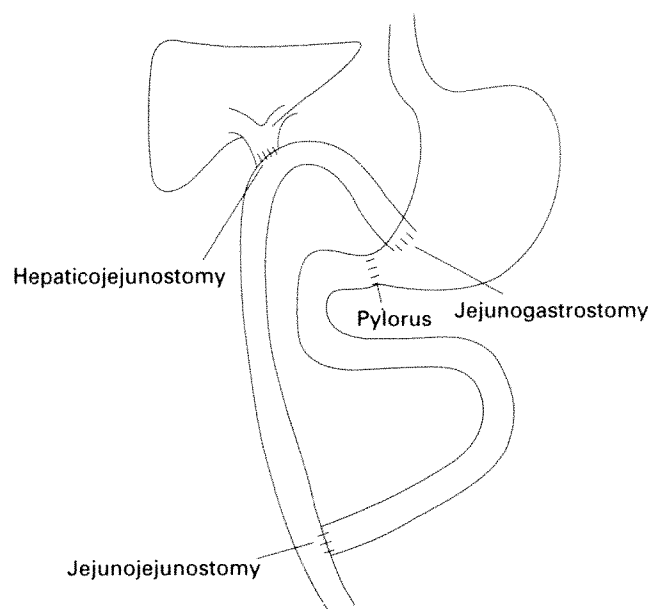


Fig. 1 Reconstruction after Roux-en-Y hepaticojejunostomy showing the jejunogastrostomy for endoscopic access

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of the gastric antrum (Fig. 1). The anastomosis is performed in one layer. The jejunogastrostomy is located approximately 10 cm from the hepaticojejunostomy.

Ten patients have undergone this procedure along with hepaticojejunostomy since October 1994. The access loop was reserved for those in whom biliary intervention was anticipated in the postoperative period, and patients in whom the surgeon was unhappy with the anastomosis.

Results

Three patients died early in the postoperative period, the remainder being followed up for between 3 and 24 months. The access loop was entered easily with the gastroscope (Olympus XQ30, P10 or videoendoscope; Shinjuku-ku, Tokyo, Japan) in five patients in whom it was attempted. In four patients, the biliary enteric anastomosis was visualized easily and was widely patent. In the remaining patient, the strictured hepaticojejunostomy was not easily visualized and biliary dilatation was not possible because the first hepaticojejunostomy had been performed close to the mesenteric border of the jejunum.

Bile gastritis has not been a clinical problem. One patient developed an asymptomatic anastomotic ulcer at the gastrojejunal anastomosis and is being followed up. Stomach contents do not enter the access loop as long as the normal pyloroduodenal channel is intact.

Discussion

Non-surgical access to a hepaticojejunostomy is sometimes required during follow-up to dilate a strictured anastomosis or to extract intrahepatic stones. It is suggested that the addition of a gastric access loop via a jejunogastrostomy to a hepaticojejunostomy is safe and may have a place in the management of biliary complications in these patients.

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Comparison of endoanal magnetic resonance imaging with surgical findings in perirectal sepsis

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Background A small percentage of patients presenting with perirectal sepsis will have complicated or recurrent disease. In these cases, clinical examination may be difficult or unreliable and accurate preoperative imaging may be of value

Methods A prospective study using a specially designed internal coil for magnetic resonance imaging (MRI) was carried out in ten patients with simple cryptogenic perirectal sepsis and in 11 patients with complex recurrent disease. Fistulas and abscesses were classified independently by a colorectal surgeon unaware of the results of MRI and a radiologist unaware of the operative findings.

Results In patients with simple perirectal infection, endoanal MRI accurately detected all abscesses and four of five fistulas. In complicated cases (multiple recurrences, sepsis secondary to inflammatory bowel disease or where the fistula track(s) traversed the main sphincter complex), endoanal MRI identified six of seven abscesses with confirmation of abscess site and horseshoe configuration when present in all cases. Surgical and radiological concordance was present in 12 of 14 fistulas with identification by MRI of the internal opening in nine of 12 cases.

Conclusion Endoanal MRI provides high-resolution images of the relationship of collections and tracks to the levator plate and is recommended in the evaluation of complex or recurrent perirectal sepsis.

The majority of anal fistulas are simple in nature and may be assessed accurately during clinical examination by an experienced coloproctologist¹. Up to 15 per cent of cases are complex, however, either by virtue of their aetiology or because of their anatomical complexity and relationship to the main sphincter muscle mass, and in these cases clinical examination may be misleading. An accurate method of preoperative imaging to delineate primary and secondary tracks and collections as well as the site of the internal opening may help to prevent further recurrence and inadvertent sphincter injury. The resolution of endoanal ultrasonography is often insufficient to delineate fistulous tracks and the rectal distension caused by the probes may distort and compress such tracks and the site of the endoanal opening.

The authors have described previously the use of a dedicated endoanal coil for high-resolution magnetic resonance imaging (MRI) to assess the anorectal sphincter in normal subjects², those presenting with faecal incontinence who have external sphincter defects³ and in patients with low rectal cancer⁴. This prospective study was undertaken to compare the accuracy of endoanal MRI with operative findings in patients with simple and complicated perirectal sepsis, and to define whether the additional anatomical information obtained by preoperative imaging may be of benefit in the operating room.

Patients and methods

There were two groups of patients in the study. Group 1 comprised unselected patients with cryptogenic perianal sepsis referred from the Accident and Emergency department of this hospital. None of these patients had previously undergone any form of anorectal surgery. There were ten patients (seven men), of median age 38 (range 25–63) years. Patients in group 2 were those deemed to have complicated perirectal sepsis. There were 11 patients (seven men), of median age 32 (range 18–56) years. Six patients had perianal Crohn's disease, two had Behçet's disease and three had complex recurrent cryptogenic sepsis. All patients had had surgery previously to deal with their anorectal sepsis with a median of three (range 2–24) previous operations.

Complicated anal fistulas were defined as all fistulas other than simple superficial, intersphincteric or low trans-sphincteric fistulas in accordance with Marks and Ritchie⁵ and Van Beers *et al.*⁶. Cases of recurrent cryptogenic sepsis where a translevator, suprasphincteric or extrasphincteric component was present and cases of perirectal sepsis secondary to inflammatory bowel disease were included. All fistulas and abscesses were classified according to the method of Parks *et al.*⁷ as intersphincteric, trans-sphincteric, suprasphincteric or extrasphincteric.

All patients tolerated MRI without the need for sedation. The mean imaging time was 40 min. Preoperative imaging was performed in both groups of patients using a specially designed endoanal coil. The details of the coil have been described previously^{3,4,8}. The outer diameter of the coil is 12 mm and the length is 75–90 mm to include the full length of the anal sphincter. Insertion of the coil was performed with the patient in the left lateral position and imaging was conducted with the patient supine. Movement artefact was prevented by an external clamp which maintained the coil in position across the anal canal.

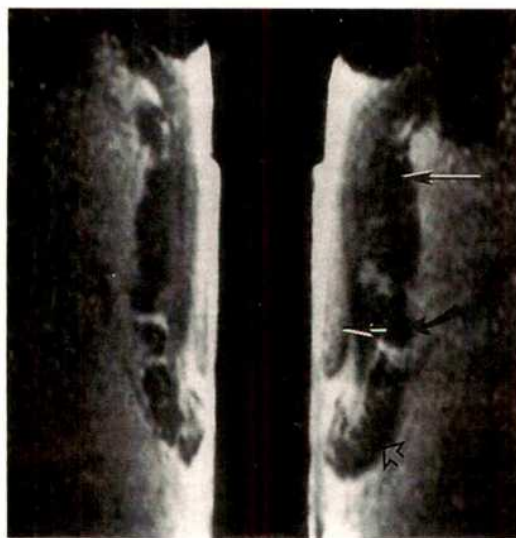
Images were obtained using 1.0-T HPQ Vista and 0.5-T Asset scanners (Picker International, Highland Heights, Ohio, USA). Standard imaging in the axial plane used T1-weighted spin-echo (SE 720–820/20 ms (TR/TE)), T2-weighted spin-echo (SE

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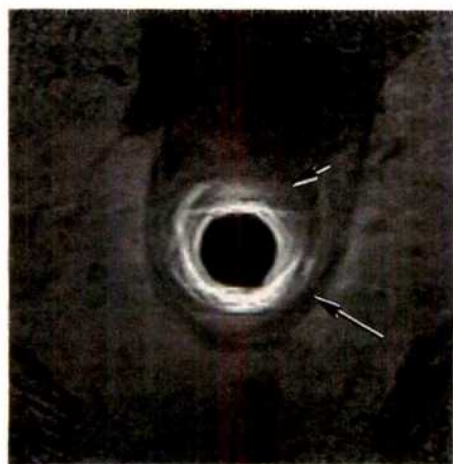
2500/80 ms (TR/TE)) and short tau inversion recovery (2500/30/110–30 ms (TR/TE/TI)) sequences. Images transverse and coronal to the anal canal in 3-mm contiguous slices were obtained with a 192 × 256 matrix, 2–4 signal acquisitions and a 10–12-cm field of view. An example of the normal appearance is shown in Fig. 1. Intravenous gadopentate dimeglumine 0.1 mmol per kg body-weight was used for contrast enhancement in all cases.

Fistulas and abscesses were classified independently by a colorectal surgeon (W.A.K.) and by a radiologist (N.M.deS.) experienced in the use of the endoanal coil. In group 1, surgery was performed with the surgeon unaware of the findings of MRI. In group 2, magnetic resonance images were kept in the operating suite for consultation by the surgeon after operative classification so that additional information provided by imaging could be used at the time to avoid further surgery.

All patients were followed for a minimum of 6 months after operation.



a



b

Fig. 1 T1-weighted coronal (a) and transverse (b) images of the normal anal sphincter complex. a Shows the homogeneous internal sphincter (short arrow) and external sphincter with its three components: subcutaneous (open arrow), superficial (curved arrow) and deep (long arrow). b Shows the normally high signal intensity of the internal anal sphincter (short arrow) and the appearance of the normal external anal sphincter (long arrow).

Results

Group 1

Details of patients in group 1 and the concordance between MRI and operative findings are shown in Table 1. At operation, all patients had abscesses whose presence and site were identified by MRI. Abscess collections in this group were intersphincteric (six cases), ischiorectal (two) and mixed (two). Five patients had fistulas (two trans-sphincteric, three intersphincteric); MRI correctly identified the presence and site of a fistula track in four cases. The internal openings of these fistulas were clearly seen in all cases. MRI missed one low fistula where the internal opening was below the level of the dentate line because the field of view of the images was not low enough. Images from a patient with an intersphincteric abscess and a low trans-sphincteric fistula are shown in Fig. 2.

Group 2

Seven abscesses and 14 fistulas were identified at operation in the 11 patients (Table 2). In five of the seven patients with abscesses, the collection was supralelevator and in two it was intersphincteric. Of the 14 fistulous tracks identified, five were extrasphincteric, five trans-sphincteric and four rectovaginal. MRI confirmed the presence of six of the seven abscesses. The site of these abscesses and the horseshoe configuration present in four cases were correctly predicted by MRI in all instances. MRI confirmed the presence of 12 of the 14 complex fistulas (Fig. 3). One supralelevator abscess with an associated extrasphincteric fistula clearly evident at operation was missed by MRI because the collection was

Table 1 Concordance between findings at surgery and magnetic resonance imaging in patients with simple fistula *in ano* (group 1)

	n	Concordance		
		Presence	Site	Position
Abscess	10	10 of 10	10 of 10	
Intersphincteric	6			
Ischiorectal	2			
Mixed	2			
Fistula <i>in ano</i>	5	4 of 5	4 of 5	
Intersphincteric	3			
Trans-sphincteric	2			
Internal opening				4 of 5

Table 2 Concordance between findings at surgery and magnetic resonance imaging in patients with complex fistula *in ano* (group 2)

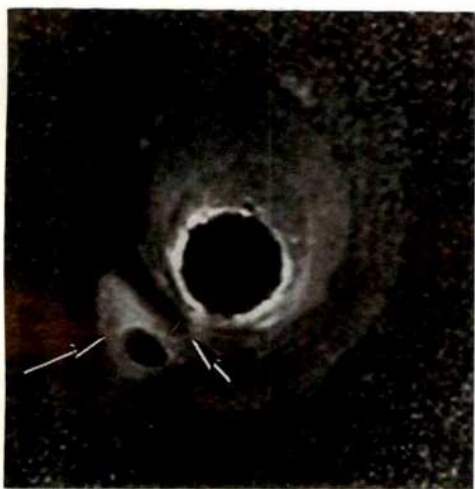
	n	Concordance		
		Presence	Site	Position
Abscess	7	6 of 7	6 of 6	
Supralelevator	5			
Intersphincteric	2			
Fistula <i>in ano</i>	14	12 of 14	12 of 12	
Extrasphincteric	5			
Trans-sphincteric	5			
Rectovaginal	4			
Internal opening				9 of 12
Horseshoe configuration	4	4 of 4		



a



b



c

Fig. 2 Transverse T1-weighted images before (a) and after (b) contrast enhancement with gadopentate dimeglumine, and short tau inversion recovery images (c) in a patient with a cryptogenic intersphincteric abscess. There is a low trans-sphincteric fistula (short arrow) entering the anal canal at the 7 o'clock position with an enhancing central abscess cavity (long arrow) containing gas



Fig. 3 T2-weighted transverse image in a patient with Behçet's disease who had eight previous procedures. A rectovaginal fistula is seen on the left (arrow)

located beyond the field of view of a 75-mm endoanal probe. Subsequently all patients were imaged using a longer 90-mm probe.

In one patient an extrasphincteric fistula was missed by the surgeon. This patient with perianal Crohn's disease had had 15 surgical procedures for recurrent perianal sepsis. At operation on this occasion one extrasphincteric fistula was found. A second small contralateral external pit was present but after tentative probing it was decided not to persist for fear of creating a false track. When the magnetic resonance images were consulted in the operating room, it was clear that there was an extrasphincteric fistula at this site. The pit was probed and the presence of a fistula was confirmed; the fistula was treated with a translevator draining seton.

In three patients, the site of the internal opening was not identified by MRI.

No patient from either group has presented with recurrent perirectal sepsis after a minimum of 6 months' follow-up.

Discussion

It is known that most recurrences after surgery for simple fistula *in ano* are a consequence of missed primary tracks and failure to identify primary openings⁹. In simple cryptogenic sepsis endoanal MRI had high accuracy in the identification of abscesses and their anatomy with respect to the sphincter musculature. Fistulous tracks were clearly identifiable in most cases provided that scanning was carried low enough.

The complex cases in this study showed a good concordance between MRI and findings at surgery for detecting the presence of abscesses (six of seven) with complete concordance for abscess site (six of six) and the presence of horseshoe extension (four of four). In patients presenting with fistula, concordance was high (12 of 14) with one extrasphincteric fistula missed by the surgeon and one by MRI. In the former case, the preoperative images aided the surgeon in confidently probing an extrasphincteric fistula in a patient who had already had 15 previous operations for unresolved perianal Crohn's

disease. Follow-up of this patient has not yet revealed recurrence. In one further patient, a lateral extrasphincteric fistula with an extensive supralelevator abscess secondary to Crohn's disease was missed by MRI. This was one of the earliest patients studied where probe placement and field of view chosen were suboptimal. In patients with a complex fistula where endoanal MRI is unable to resolve the internal opening in the subepithelial layer, the site of the internal opening can only be inferred by the relationship of intersphincteric disease to the mucosa nearby. It may be that the presence of the endoanal probe compresses the opening and obscures detection. Nevertheless, demonstration of the internal opening with endoanal MRI appears to be superior to that using an external coil¹⁰.

Several modalities have been evaluated previously to define the anatomy of fistula *in ano*. Fistulography, although accurate in identifying primary and secondary tracks as well as internal openings, fails to define their relationship to the puborectalis sling. In addition, the procedure is painful and has the risk of spreading perirectal infection^{11,12}.

Computed tomography of fistula has proved disappointing because of an inability to resolve tracks and collections in the ischiorectal fossae and to outline clearly their relationship to the levator plate. Furthermore, old burnt out tracks and scar tissue are difficult to differentiate^{13,14}. Gluteal and pudendal vasculature may simulate inflammatory tracks and partial volume averaging of muscle-fat interfaces may mimic streaking normally associated with active inflammation¹⁵.

Endoanal ultrasonography is of limited benefit in detecting whether there is supralelevator/suprasphincteric sepsis and in identifying lateral ischiorectal/extrasphincteric infection. These two conditions are precisely the occasions in which the colorectal surgeon requires additional anatomical information about the complexity of the fistula. In disease extending above the anorectal ring, poor acoustic coupling between the endoanal probe and the rectal wall prevents definition. In laterally placed disease, which is frequently associated with the external opening of extrasphincteric fistulas, the focal distance of the ultrasound probe is often exceeded^{16,17}. Also, one of the innate properties of the ultrasonographic technique, the phenomenon of acoustic impedance and shadowing, may overestimate a large intersphincteric collection as trans-sphincteric, placing the external sphincter at risk¹⁸.

Endoanal MRI will still be limited by technical difficulties facing any form of endoluminal imaging, most notably by the distance of disease from the probe. There is a rapid fall off of signal from the surface of the coil radially with a gain in signal-to-noise ratio over standard phased array images up to 2 cm from the surface of the coil². Although the perianal and ischiorectal fossae are well visualized up to 5 cm from the coil centre and a coil of 90 mm in length will display the entire longitudinal extent of the sphincter, disease which lies outside this range will not be detectable. Furthermore, luminal stenosis may prevent accurate placement of the probe. A combination of endoanal coil and external coil MRI in the surgical management of patients with complex recurrent fistula *in ano* awaits larger comparative studies.

It is recommended that endoanal MRI be used by the coloproctologist in complex cases where clinical exami-

nation may be limited or misleading and in identifying those patients in whom the sphincter mass is at risk. It is anticipated that accurate preoperative definition of these cases may also expand the indications for complex endoanal surgery, in particular use of the anal advancement flap¹⁹.

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For debate

The reduction of uncertainty

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Information use has been defined as the reduction of uncertainty. Applied to medicine this may include access to guidelines, decision support and on-line published material. Information should be both about patients and for patients. It is unusual for hospital doctors to have appropriate clinical information available at the point of patient contact. Some may be fortunate enough to have an organized medical records department that is able to locate paper records at any hour. Very few have this information in computerized form. The provision of information for patients can be haphazard and doctors may be unaware of the content of some of the available material.

Many surgeons use locally created systems to collect data, and the use of this material for local audit purposes is well recognized^{1,2}. Surgeons were among the first to apply scoring methods to assess outcome of treatment³, to develop an illness severity score for transmission and comparison⁴, and to use computers to develop the severity score into an outcome prediction⁵. Nurses now make frequent use of dependency scores and are much involved in data collection. A residual problem is the collection of clinical data that can be transmitted and exchanged or compared across units.

The comparative audit organized within the Royal College of Surgeons of England attempts to fulfil this function⁶ but this is dependent on individuals collecting and returning data. There is a need, however, to structure information and to have a common terminology to allow comparison of like with like. Any attempt to compare outcomes will fail unless the collected information includes a severity assessment. The data must also be in such a form as to be compatible with the information on long-term outcome available on computers used in general practice. Properly structured information should therefore be readily available to hospital and primary care teams.

General practitioners in the UK quickly recognized the need for structured data and a system to code the huge breadth of material. Read developed terms to make the discipline of structuring data acceptable and published the evaluation with Benson⁷. When applied to hospital medicine the necessary depth of detail was missing. The clinical terms project allowed the professions (including professions allied to medicine and nursing) to backfill the Read thesaurus to provide this necessary depth⁸. The initial work is complete but it is recognized that the editing and updating must be a continuous process. The Comité Européen de Normalization (CEN) has a technical committee CEN/TC 251 working to draw up medical informatics pre standards which allow the structuring of data for transmission. The output has yet to

exert influence on clinical systems and structured information collection in the UK.

Work has been done under the auspices of the National Health Service Executive Information Management Group to look at the structure of clinical information and at the context, such as certainty of diagnosis, past history and family history, in which the clinical terms would be used. Definitions of main diagnosis and operation are an essential part of structured data collection but there is still no nationally agreed definition of main operative procedures. Even the concept of 'an operation' may be dated. The UK Office of Population Censuses and Surveys' classification of surgical operations and procedures fourth revision (OPCS 4) still implies that local or general anaesthesia should be used, that a theatre is necessary and that a surgeon should have done the deed⁹. Endoscopic and endovascular procedures, thrombolysis and outpatient interventions may not be captured. Perhaps the evolving Australian concept of procedures has something to offer, describing them as invasive diagnostic, invasive therapeutic, non-invasive diagnostic, non-invasive therapeutic, and cognitive¹⁰.

Surgical trainees and consultants need to be introduced to discipline in the use of terms that will provide accurate data and avoid confusion by data coders. For example, a child 4 years of age does not have an inguinal hernia repair but a herniotomy. There should, perhaps, be a specific module on structured information and its relationship to audit in the curriculum for basic surgical training. Having collected accurate and certain data, they must then be transmitted and shared with other professions. Leaving aside the important issue of confidentiality, issues of structure are again important. For example, a message about endoscopy to exclude malignancy, which did not make the context of uncertainty clear to the recipient system, could produce confusion.

Primary care computerized systems are already in use in the UK for clinical information and for item of service reimbursement. Why should computerization have succeeded in this environment and not in the hospital sector? The systems are often quite simple and organized around the primary care team. Hospital doctors fortunate enough to be consulted about a hospital system immediately expect enormous complexity and often lose sight of the need to structure recorded data. Decision support is sought and when 'wish lists' are combined with business needs the result can become cumbersome and unworkable. The current trend for trainees to use personal organizers for data collection has several problems, not least that of confidentiality of patient data. The information collected is often incomplete and the need to register as a data user under the Data Protection Act may be neglected. The Audit Commission¹¹ recommended the avoidance of multiple entry of the same data and this is exactly what trainees using personal organizers find themselves doing. The collection of complications in such systems is often incomplete and unlinked to procedures.

The solution must be the creation of clinical systems, capable of sharing useful and structured clinical information with other users, particularly nursing and professions allied to medicine, avoiding the reduplication of

data entry. If this clinical information matches the structure of that in the community, the holy grail of readily available information to give surgeons feedback on long-term outcome may not be too far distant. This feedback may provide answers to questions being asked by patients and purchasers of healthcare. Uncertainty will have been reduced.

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Changing trends in the management of pheochromocytoma

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Background The recent experience of a specialist endocrine surgery unit in the management of pheochromocytoma is reviewed.

Methods Over a 14-year period (June 1978 to June 1992) 43 patients (14 men, 29 women) with a mean age of 42 years were referred with pheochromocytoma.

Results Biochemical confirmation was usually by measurement of 24-h urinary vanillylmandelic acid. From 1980 venous sampling was replaced by computed tomography as the primary localizing procedure. ¹³¹I-meta-iodobenzylguanidine scintigraphy was used in all patients between 1984 and 1987, but selectively after that. With regard to the operative approach used, between 1978 and 1983 midline or flank incisions were used, and from 1984 to 1992 subcostal or posterior approaches were used predominantly. There was one operative (30-day) death. One patient died 24 months after operation from recurrent malignant pheochromocytoma, and three patients died during follow-up from unrelated causes. The remaining patients (mean follow-up 30 months) have no evidence of recurrent pheochromocytoma, although four remain on antihypertensive medication.

Conclusion Improved imaging of pheochromocytoma obviates the need for transperitoneal exploration, allowing selected pheochromocytomas to be successfully managed using an extraperitoneal approach.

The first surgical excision of a pheochromocytoma was reported in 1927 by Roux¹ who described removal of an adrenal mass in a patient who had a 2-year history of episodic vertigo and nausea. Soon after, Mayo² reported excision of a retroperitoneal tumour of neural origin associated with paroxysmal hypertension. In many patients the clinical syndrome due to excess catecholamine secretion occurs in a paroxysmal fashion, occasionally causing sudden death. The risk previously associated with surgical excision of pheochromocytoma³ has been reduced by better appreciation of the pathophysiology of this disorder leading to improved pharmacological perioperative management. Advances have also been made in the preoperative radiological and biochemical evaluation of these tumours and in various aspects of their surgical management. In this study, recent experience in the management of pheochromocytoma is reviewed; changes in preoperative assessment and perioperative management are highlighted.

Patients and methods

Over the 14 years from June 1978 to June 1992, 43 patients were referred to the authors' department for operative treatment of pheochromocytoma. There were 14 men and 29 women with a mean age of 42 (range 16–73) years. The main presenting symptoms are shown in Table 1. In 19 patients symptomatic episodes were either paroxysmal or episodic, or labile hypertension was noted. In two patients hypertension was first noted during anaesthesia for unrelated procedures. The mean duration of symptoms before diagnosis was 30 (range 0–120) months. Mean (s.d.) systolic blood pressure was 171(44) mmHg and mean diastolic blood pressure was 105(25) mmHg. Nine patients had multiple endocrine neoplasia (MEN) II; three had neuroectodermal dysplasia (two neurofibromatosis, one von Hippel-Lindau disease); and in three pheochromocytoma was

identified during investigation or follow-up of an unrelated malignancy (ovarian, testicular, and follicular thyroid cancer).

The diagnosis was usually confirmed by demonstration of raised 24-h urinary vanillylmandelic acid (VMA) output on three occasions. In some cases serum and urinary catecholamines were also measured, and in a few patients with equivocal results a pentolinium or clonidine suppression test was performed^{4,5}. Radiological localization was by venous sampling or, more recently, computed tomography (CT) and ¹³¹I-meta-iodobenzylguanidine (MIBG) scintigraphy⁶.

A standard protocol for preoperative adrenergic blockade was used. All patients received the α -adrenergic blocker phenoxybenzamine for 1 week before operation, starting at a dose of 40 mg day⁻¹ and gradually increasing to 80–120 mg day⁻¹. Over the final 2 or 3 days, intravenous fluids were given to compensate for expansion of the intravascular space. β -adrenergic blockade with propranolol was instituted after α -blockade was established if tachycardia or other evidence of cardiac dysrhythmia developed. Adrenergic blockade was stopped immediately after operation.

All tumours were submitted to histopathological examination including immunohistochemical staining for neuroendocrine markers. The majority of patients have been followed up at this hospital with serial VMA measurements although some, particularly those referred from overseas, have been followed at their referring hospital.

Table 1 Presenting features in 43 patients with pheochromocytoma

Symptom	n
Hypertension	24 (56)
Headache	24 (56)
Sweating	20 (47)
Palpitations	14 (33)
Dizziness	6 (14)
Congestive cardiac failure	5 (12)
Hypertension during anaesthesia	3 (7)
Impaired glucose tolerance	3 (7)
Screened (six MEN II, three incidental)	9 (21)

Values in parentheses are percentages. MEN, multiple endocrine neoplasia

Results

Biochemical confirmation of pheochromocytoma

Urinary VMA levels at 24 h were measured in all but one patient, with a mean(s.d.) preoperative value of 128(141) mg per 24 h. Urinary VMA levels were raised in all but four patients (sensitivity of 90 per cent). Serum adrenaline and noradrenaline were measured in 14 patients and urinary catecholamines or metanephrines were measured in nine patients. These measurements were abnormally raised in all cases. A clonidine or pentolinium suppression test was used in five patients and was positive in all five.

Radiological localization

Venous sampling for catecholamines was used in nine patients. In one patient venous sampling suggested that bilateral adrenal tumours were present and at operation a tumour was identified in the left adrenal only. A further two patients underwent negative exploration following false-positive venous sampling. Pheochromocytomas were correctly localized in all 40 patients who underwent CT after 1979. MIBG scanning was used in 17 patients, including all patients between 1983 and 1988, and in selected patients from 1989 to 1992. Tumours were correctly identified in 15 patients. The MIBG scan was negative in one patient, and in another patient bilateral abnormalities were present on MIBG, although a tumour was only located in the left adrenal.

Anaesthetic and operative management

Mean blood pressure on induction of anaesthesia was 136/76 mmHg. Only four patients had systolic blood pressure greater than 180 mmHg at induction. Intraoperative administration of supplemental adrenergic agents (either phentolamine or labetalol) was required in 18 patients and sodium nitroprusside infusion was used in only three patients. No adverse events occurred as a result of intraoperative fluctuations in blood pressure. Postoperative administration of inotropic agents to correct hypotension due to catecholamine withdrawal was required in one patient for less than 24 h.

Based mainly on improvements in available imaging techniques, the operative approaches used changed considerably over the time period reported. The incisions

used are shown in *Fig. 1*. Before 1984 midline or, less frequently, flank incisions were used in all patients. Since 1984 a subcostal rather than a midline incision was used for the majority of large (more than 5.0 cm), ectopic or malignant tumours. A median sternotomy was added in one patient. During the later years studied, a posterior approach has been used in selected patients with tumours less than 5.0 cm in diameter, localized to the adrenal (*Fig. 1*). In one patient a subcostal incision with a median sternotomy extension was used for removal of a tumour which extended along the adrenal vein into the vena cava.

The mean diameter of all pheochromocytomas excised was 4.9 (range 2.0–13.0) cm. The mean diameter of the nine tumours excised through a posterior approach was 3.5 (2.0–4.5) cm.

A 60-year-old woman died within 24 h from excision of a 4.0-cm pheochromocytoma complicated by development of a pneumothorax. Autopsy showed left ventricular failure, and immunohistochemical examination of the tumour demonstrated typical features of a pheochromocytoma and also immunoreactivity for adrenocorticotrophic hormone (ACTH). This raised the possibility that adrenocortical insufficiency contributed to the patient's death although this could not be confirmed biochemically.

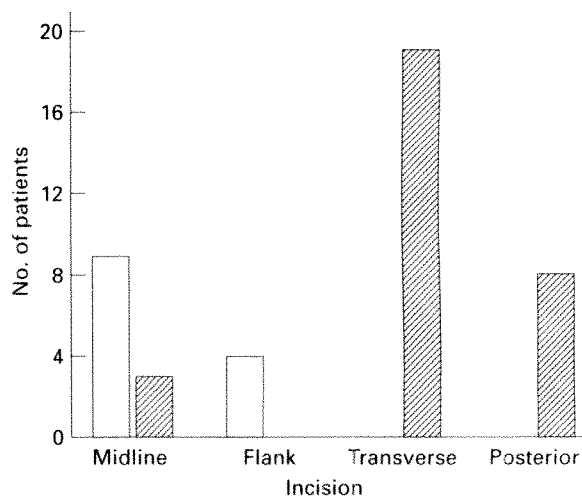


Fig. 1 Incisions used from 1978 to 1983 (□), and from 1984 to 1992 (▨)

Table 2 Operative approach and postoperative stay, units of blood transfused, and complications

Approach	No. of patients	Postoperative stay (days)*	Units of blood transfused*	Complications
Midline	12	16 (9–40)	3.0 (0–8)	Splenectomy 3 Respiratory tract infection 1 Pneumothorax 1 Adhesion obstruction 1 Wound sepsis 1
Lateral	4	14 (9–20)	1.0 (0–2)	Pneumothorax 1 Wound sepsis 1
Subcostal	19	9 (7–12)	0.4 (0–4)	Respiratory tract infection 1 Splenectomy 1 Pneumothorax 1
Posterior	8	11 (6–25)	1.0 (0–4)	Respiratory tract infection 2 Pneumothorax 1 Postoperative bleeding 1

*Values are mean (range)

Intraoperative splenic injury necessitating splenectomy occurred in three patients and four had pleural drains inserted following inadvertent opening of the pleural space. Table 2 shows postoperative complications.

Follow-up

Mean follow-up for the entire group was 31 (range 9–120) months. Mean(s.d.) systolic blood pressure was 119(29) mmHg and mean(s.d.) diastolic blood pressure was 79(19) mmHg. Mean(s.d.) 24-h urinary VMA level after operation (usually measured within 3 months of operation) was 27(11) per mg 24 h.

Four patients required long-term medication for persistent hypertension following operation. Urinary VMA levels at 24 h were normal or only mildly raised in all four. Further biochemical and radiological assessment, including clonidine or pentolinium suppression testing, failed to detect recurrent pheochromocytoma and all four remain under regular outpatient review.

Four patients have died during follow-up. One patient died 2 months after operation from mesenteric infarction. The patient with ovarian carcinoma died 24 months after pelvic clearance and excision of pheochromocytoma. One patient with a malignant pheochromocytoma died 31 months after operation; another with von Hippel-Lindau syndrome died with a cerebellar haemangioblastoma 10 years after excision of a pheochromocytoma.

Discussion

This study highlights some of the continuing problems with the management of pheochromocytoma. These are rare tumours which frequently present with atypical symptoms that may mistakenly be ascribed to a variety of disorders⁷. Clinical suspicion remains the single most important factor in the identification of pheochromocytoma. This series differs from earlier reports from the UK in that almost 25 per cent of tumours were asymptomatic and were identified by screening of families with MEN II, or were detected incidentally during investigation of other complaints⁸.

Opinion is divided as to the best biochemical test for confirmation of excess secretion of catecholamine. Measurements of urinary catecholamines or their metabolites at 24 h (either metanephrines or VMA) are all relatively easy to perform. However, difficulties in obtaining a complete collection and the need to impose dietary control have led to some dissatisfaction with these methods. Plasma catecholamine levels have been reported by some groups to be as sensitive as 24-h urinary measurements in the diagnosis of pheochromocytoma⁹. However, great care must be exercised in the collection of plasma levels as spurious rises in plasma catecholamines may be produced if the patient experiences any discomfort or apprehension at the time the samples are taken. Although the reported sensitivity of urinary VMA estimation varies widely from 40 to 90 per cent, the experience from the authors' unit has been satisfactory, with a previously reported sensitivity of greater than 95 per cent⁸. For this reason the authors continue to use urinary VMA for initial screening of patients and post-operative follow-up. Measurement of both urinary and serum catecholamines and their metabolites in all patients is unnecessary and expensive and should be reserved for equivocal cases, as should pharmacological suppression tests.

Clear trends in diagnostic imaging of these tumours emerged over the study period. Venous sampling was the favoured technique during the earlier years of the study¹⁰. However, it is invasive and time-consuming and occasionally produces false-positive results leading to negative exploration. As a result it was rapidly superseded by CT when it became available. Isotope scintigraphy with MIBG became available in 1983 and over the following 5 years was shown to be highly sensitive⁶; in agreement with other published series, we have found that the precise anatomical information provided by CT has prevented MIBG scanning from fully replacing CT¹¹. MIBG scanning is not now performed routinely in this unit. However it has been used for patients in whom CT suggests that there may be multiple or extra-adrenal tumours or in patients with elevated urine or serum catecholamines in whom CT is normal. MIBG scanning is also useful in surveillance and follow-up of patients with the MEN II syndrome. A good correlation has been demonstrated between the degree of MIBG uptake and the evolution of adrenal medullary hyperplasia into frank neoplasia, allowing serial MIBG scanning to be used to select the appropriate timing for surgery in this subset of patients¹².

Although a variety of operative approaches to the adrenal gland has been described, the conventional surgical wisdom is that an anterior, transperitoneal approach should be used for excision of pheochromocytomas^{11,13}. This is based on the observation that approximately 10 per cent of tumours are extra-adrenal and 10 per cent are multiple. The greater resolution of the newer generation of CT scanners, augmented by the sensitivity of MIBG scintigraphy, eliminates the need for an extensive transperitoneal exploration. It is suggested that, in selected cases, adrenalectomy for pheochromocytoma may safely be performed through a posterior incision. Tumours that have been localized to the adrenal and are less than 5.0 cm in diameter are suitable for this approach. By these criteria, since 1984, only eight patients have been considered suitable for a posterior approach. None of these patients has required re-exploration for missed tumour. Reported experience with the posterior approach for adrenalectomy suggests that patients mobilize more rapidly, are less prone to respiratory complications, and may be discharged earlier than those in whom an anterior approach is used^{13,14}.

Perhaps the most important feature of this report is that it demonstrates the safety and efficacy of excision of pheochromocytoma without extensive transperitoneal exploration in selected patients. This has important implications for the application of laparoscopic adrenalectomy for pheochromocytoma. This new technique offers the possibility of even more rapid recovery and earlier discharge from hospital following adrenal surgery^{15,16}. Concerns about the inability to explore the retroperitoneum at laparoscopy are unfounded because of the high sensitivity and specificity of CT and MIBG scanning as demonstrated by this and other reports¹¹. Further experience with laparoscopic excision of pheochromocytoma is required before its potential can be realized and its limitations recognized.

The correct management of adrenal disease in patients with MEN II has also been the subject of some controversy. Van Heerden *et al.*¹⁷ suggest that bilateral adrenalectomy should be performed once any adrenal medullary abnormality, including adrenal medullary hyperplasia, is identified in these patients. The experience

from other centres, including this unit, supports a more conservative approach advocating adrenal preservation where possible with bilateral adrenalectomy being performed only if bilateral tumours are identified radiologically or by palpation at operation^{18,19}. In this series, three of nine patients with MEN II had bilateral adrenalectomy (for bilateral tumours), the remaining six who underwent unilateral adrenalectomy have no evidence of pheochromocytoma in the contralateral gland with a mean follow-up of 64 (range 9–120) months. Serial MIBG scanning is especially useful in following these patients¹².

Better preoperative preparation by α -adrenergic blockade has obviated much, but by no means all, of the risk associated with excision of pheochromocytoma. The duration of preoperative adrenergic blockade varies in different reported series; the present authors used 1 week only with satisfactory results. Blood pressure had been normalized in most of the patients before operation and, although further intraoperative administration of hypotensive drugs was required in some patients, no adverse events occurred. A recent report from Orchard *et al.*¹¹ at the Mayo Clinic noted no difference in intraoperative blood pressure control in patients prepared for less than 7 days compared with those prepared for more than 7 days. An alternative to α -blockade is calcium channel blockade either alone or in combination with phenoxybenzamine for patients with pheochromocytoma. Some authors^{20,21} claim that this combination prevents many of the intraoperative fluctuations in blood pressure that occur during tumour handling and may minimize blood pressure collapse after tumour removal. In general, series which report the use of calcium channel blockers with adrenergic blockers seem to demonstrate favourable results although further evaluation is needed since the number of patients included are relatively small. One report suggests that calcium channel blockers used alone may not provide sufficient protection against blood pressure lability²².

The long-term outlook for patients with pheochromocytoma remains very good. As in other reported series^{8,11}, a number of the present patients required antihypertensive medication following operation but, as yet, none of these has developed biochemical evidence of recurrent pheochromocytoma. Patients with MEN II who undergo unilateral adrenalectomy constitute a particular group in whom rigorous follow-up is mandatory.

Pheochromocytoma continues to present considerable diagnostic and management problems which, because of the rarity of this tumour, are best dealt with in a centre with a special interest in endocrine surgery. Greater confidence in the accuracy of radiological localization should allow excision of a greater proportion of these tumours through a posterior incision or by laparoscopic adrenalectomy.

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Risk factors for rebleeding and death from peptic ulcer in the very elderly

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Background Ageing populations are increasing in many countries and bleeding peptic ulcers in patients older than 60 years carry a greater risk of rebleeding and death. This study aimed to identify the risk factors for rebleeding and death in very elderly patients with peptic ulcer bleeding. The efficacy of treatment in preventing recurrent bleeding and death in this group of patients was also studied by means of prospective data collection and analysis.

Methods Data relating to 1744 patients treated between September 1985 and January 1994 for peptic ulcer bleeding were collected prospectively and analysed. Patients were stratified by age to one of three groups: group 1 (less than 60 years, $n = 833$), group 2 (60–79 years, $n = 706$) and group 3 (80 or more years, $n = 205$).

Results Univariate and multivariate analyses of 21 factors possibly affecting either rebleeding or death identified age greater than 80 years as one of the factors significantly affecting rebleeding and death. In a comparison of groups 1, 2 and 3, the likelihood of rebleeding and death was significantly greater in group 3. Univariate and multivariate analyses for rebleeding and death were performed for each group. The severity of initial bleeding had a marked bearing on subsequent rebleeding rates for all three groups. In group 3, however, large ulcer size and impaired liver function were additional factors which correlated significantly with final outcome. No rebleeding or morbidity occurred when endoscopic treatment was performed early for patients in group 3 but there was a significantly greater risk of further recurrent haemorrhage and treatment-related morbidity when treatment was performed after the onset of rebleeding.

Conclusion Patients aged 80 years or greater had the highest risk of rebleeding and death. For patients below 80 years of age, significant factors related to a fatal outcome included co-morbid illness, complications and the need for mechanical ventilation. For patients aged 80 years or older, the significant factors were ulcer size greater than 2 cm and admission with serum bilirubin level above 20 mmol/l. Endoscopic treatment for the very elderly was effective if carried out early.

Many parts of the world are experiencing an increase in ageing populations. In 1988 it was estimated that 10 per cent of a given population were older than 65 years and that by the year 2000 this proportion would increase to 15 per cent¹. Physiological responses to stress from illness vary with age and elderly patients may not be able to meet increased metabolic demands. Even amongst the elderly, differences exist between a younger cohort and the very old. In this study, a younger cohort aged from 60 to 79 years was defined arbitrarily and the very elderly as being aged 80 years or older; the age limit of 60 years was chosen as this is the official age of retirement in Hong Kong.

Peptic ulcer bleeding consumes substantial resources and requires proficiency in clinical and endoscopic skills for a successful outcome. This is particularly evident in the management of elderly patients as the mortality rate increases from less than 10 per cent for those younger than 60 years to 35 per cent for octogenarians². The high mortality rate in the latter group of patients has not changed over the past 30 years despite improvements in diagnostic techniques and advances in intensive medical care and surgical strategies. A knowledge of risk factors for morbidity and death after peptic ulcer bleeding may help improve treatment outcomes. Previously, the authors have identified age greater than 60 years, previous medical illness, shock on admission, large ulcer size and endoscopic stigmata of recent haemorrhage (ESRH) as

significant risk factors for rebleeding and death³. However, specific risk factors for the very elderly remain to be established and it is with this aim that these analyses were undertaken.

Patients and methods

Between September 1985 and January 1994, 1744 patients presenting with acute bleeding from peptic ulcer were admitted into a single specialist gastrointestinal surgical unit. Patients were allocated to three groups: group 1 (aged less than 60 years), 2 (aged between 60 and 79 years) and 3 (aged 80 years or greater). All patients admitted were managed in a standardized fashion. Following initial resuscitation, upper gastrointestinal endoscopy was carried out within 24 h of admission. The location and size of any ulcerated areas were documented. Major ESRH were defined as a visible vessel with or without adherent clot, spurting or oozing haemorrhage; minor ESRH were defined as loose clots and black spots in the ulcer base. Patients without major ESRH were managed conservatively and received intravenous H_2 -receptor antagonist therapy following resuscitation. Patients with major ESRH were considered for either endoscopic treatment or immediate operation following resuscitation depending on the presence or absence of shock on presentation, co-morbid illness, rate of bleeding, and endoscopic findings including ulcer site and size. Surgical intervention was favoured in patients with shock on presentation in whom bleeding was brisk, particularly when co-morbid illness was absent, ulcer size was very large and/or access for endoscopic therapy was considered difficult. Adrenaline (1:10000) injection and/or thermal coagulation using a heater probe were employed for endoscopic therapy.

Patients were monitored serially for persistent bleeding or rebleeding. Rebleeding was defined as fresh haematemesis or

melaena, fall in systolic blood pressure (to below 100 mmHg or by 50 mmHg) or fall of haemoglobin level of 2 g/dl or more after correction of anaemia³. Patients with rebleeding after conservative or endoscopic treatment underwent operation. The emergency surgery group, therefore, comprises patients who underwent immediate operation on first presentation without initial conservative treatment and those in whom emergency operation was performed to control rebleeding.

Clinical, laboratory, endoscopic, treatment and outcome data including postoperative morbidity were collected prospectively and entered into a computer database for statistical analysis. Previous medical illness was documented as being present when the patient had a history of ischaemic heart disease, hypertension, cerebrovascular accident, diabetes mellitus, chronic obstructive airways disease, tuberculosis, chronic renal failure, cirrhosis or malignant disease. Pretreatment transfusion was defined as any transfusion before therapeutic endoscopy and/or surgery.

Risk factors for rebleeding and death were studied first for the entire group of 1744 patients and then for groups 1, 2 and 3 separately. These included 16 patient factors and five ulcer factors. The number of units of blood transfused before institution of treatment and the total number of units of blood transfusion were also included in the analysis of risk factors for rebleeding and death. The patients in group 3 were evaluated in detail with particular emphasis on the pathology of ulcers and treatment outcome.

Statistical analysis

Data were analysed using the computer software SPSS for Windows release 6.0 (SPSS, Chicago, Illinois, USA). Comparisons between groups were made using the Mann-Whitney *U* test, Fisher's exact test or χ^2 test as applicable. Multivariate analysis of treatment outcome was performed using a stepwise logistic regression model. Statistical significance was taken at $P \leq 0.05$.

Results

Of 1744 patients, endoscopic treatment was performed for 301 (17.3 per cent) and emergency surgery was undertaken in 132 (7.6 per cent). One hundred and seventeen patients (6.7 per cent) underwent early elective operation after haemodynamic stabilization. Rebleeding occurred in 276 patients (15.8 per cent) and 68 (3.9 per cent) died, 42 of whom had rebled. Rebleeding after endoscopic treatment, emergency surgery and elective surgery was encountered in 28 patients (9.3 per cent), nine (6.8 per cent) and nine (7.7 per cent) respectively. Seventy-eight patients developed complications after endoscopic or surgical treatment. Mechanical ventilation was required in 40 and parenteral nutrition in 21 patients. Twenty-six patients died after complications; the occurrence of complications significantly increased mortality rate ($P < 0.0001$).

Eight hundred and thirty-three patients (47.8 per cent), 706 (40.5 per cent) and 205 (11.8 per cent) were stratified to groups 1, 2 and 3 respectively. The male to female ratio and the location of peptic ulceration in patients in group 3 were significantly different from those in groups 1 and 2 (Table 1). Moreover, those in group 3 had significantly greater rebleeding and mortality rates, and a higher proportion died after rebleeding.

Univariate analyses of risk factors for rebleeding and death performed for all 1744 patients showed that significantly more patients rebled and died when ulceration was confined to the stomach. Of the 597 patients with gastric ulcer, 142 (23.8 per cent) and 38 (6.4 per cent) rebled and died respectively. The corresponding figures for the 905 patients with duodenal ulcer were 107 (11.8 per cent) and

24 (2.7 per cent). Moreover, rebleeding and death were significantly related to ulcer size ($P < 0.02$) and the presence of ESRH ($P < 0.01$). The mean (s.d.) ulcer size in patients who rebled was 1.8 (1.7) cm and 2.5 (1.9) cm in patients who succumbed. However, the number of ulcers was found not to have a significant effect on the likelihood of rebleeding or death.

The clinical risk factors for rebleeding and death are shown in Table 2. A history of ulcerogenic drug ingestion was not significantly related to rebleeding or death.

Table 1 Sex ratio, rebleeding and mortality rates in groups 1, 2 and 3

	Group 1	Group 2	Group 3	<i>P</i>
Total no. of patients	833	706	205	—
M:F ratio	3.9:1	2:1	1:1.4	<0.0001
Ulcer size > 2 cm	82 (9.8)	100 (14.2)	30 (14.6)	0.006
Ulcer site				
Duodenal	545 (65.4)	290 (41.1)	70 (34.1)	<0.0001
Gastric	190 (22.8)	308 (43.6)	99 (48.3)	<0.0001
Duodenal and gastric	98 (11.8)	108 (15.3)	36 (17.6)	n.s.
Rebleeding	99 (11.9)	125 (17.7)	52 (25.4)	<0.0001
Deaths				
Total	3 (0.4)	42 (5.9)	23 (11.2)	<0.0001
After rebled	2 (0.2)	23 (3.3)	17 (8.3)	<0.0001

Values in parentheses are percentages. n.s., Not significant. Mann-Whitney *U* test; Fisher's exact test; χ^2 test

Table 2 Univariate analysis of patient factors affecting rebleeding and mortality rate

	Rebleeding (<i>n</i> = 276)		Death (<i>n</i> = 68)	
	No. of patients	<i>P</i>	No. of patients	<i>P</i>
M:F ratio	2.8:1	n.s.	1.8:1	n.s.
Haematemesis and melaena	202	0.04	49	n.s.
Associated epigastric pain	96	n.s.	26	n.s.
Smoking	117	n.s.	32	n.s.
Alcohol ingestion	61	n.s.	14	n.s.
Ulcerogenic drug ingestion	49	n.s.	16	n.s.
Previous dyspepsia	30	n.s.	9	n.s.
Previous gastrointestinal bleeding	80	0.001	10	0.0001
Previous gastrointestinal operation	18	n.s.	3	n.s.
Concomitant medical illness	102	<0.0001	47	<0.0001
Previous malignant disease	6	n.s.	7	0.001
Shock†	41	n.s.	18	<0.0001
Admission pulse (per min)*	90(16)	0.009	88(21)	n.s.
Admission haemoglobin (g/dl)*	8.4(2.6)	<0.0001	7.4(2.5)	<0.0001
Admission BUN (mmol/l)*‡	16.2(10.8)	<0.0001	22.0(13.3)	<0.0001
Admission bilirubin (mmol/l)*§	12.9(30.4)	<0.0001	16.6(15.3)	<0.0001

*Values are mean (s.d.). †Fall in systolic blood pressure to below 100 mmHg or by 50 mmHg; ‡normal range 2.5–6.4 mmol/l; §normal range 7–19 mmol/l. BUN, blood urea nitrogen. Mann-Whitney *U* test; Fisher's exact test; χ^2 test

Table 3 Factors associated with rebleeding and death by multivariate analysis

	Coefficient	P	Odds ratio
Rebleeding (n = 276)			
Pretreatment transfusion > 4 units	2.29	<0.001	11.1 (8.2–15.1)
Admission haemoglobin < 10 g/dl	-0.59	0.003	1.8 (1.3–2.3)
Haematemesis and melaena	0.70	0.011	1.6 (1.0–2.5)
Admission BUN > 15 mmol/l	0.02	0.021	2.2 (1.7–2.8)
Complication	1.15	<0.001	9.0 (5.6–14.4)
ESRH	1.14	<0.001	5.1 (3.8–6.9)
Age ≥ 80 years	0.59	0.011	2.1 (1.5–3.0)
Death (n = 68)			
Concomitant medical illness	1.30	<0.001	6.8 (4.0–11.5)
Admission haemoglobin < 10 g/dl	-0.14	0.016	3.4 (1.6–6.4)
Complication	2.00	<0.001	19.3 (11.0–33.0)
Rebleeding	1.37	<0.001	10.0 (6.0–16.6)

Values in parentheses are 95 per cent confidence intervals. BUN, blood urea nitrogen (normal range 2.5–6.4 mmol/l); ESRH, endoscopic stigmata of recent haemorrhage. Stepwise logistic regression

Table 4 Factors associated with rebleeding in the three age groups, by multivariate analysis

	Coefficient	P	Odds ratio
Group 1			
Total transfusion > 4 units	0.31	<0.001	12.4 (7.6–20.3)
Group 2			
Pretreatment transfusion > 4 units	0.25	0.001	9.1 (5.8–14.3)
Group 3			
Pretreatment transfusion > 4 units	2.92	0.001	14.0 (6.4–30.3)
ESRH	1.56	0.01	4.5 (2.1–9.5)

Values in parentheses are 95 per cent confidence intervals. ESRH, endoscopic stigmata of recent haemorrhage. Stepwise logistic regression

Significant variables were identified and then further studied by multivariate analysis using a stepwise logistic regression model. Age 80 years or greater was identified as one of the factors affecting rebleeding (Table 3). Separate evaluation of groups 1, 2 and 3 by univariate and multivariate analyses identified similar factors significantly affecting rebleeding rates (Table 4). Risk factors for death amongst the very old differed, however, from those evident in younger patients. An increased risk of death was noted in patients aged less than 60 years with comorbid conditions who developed a complication, particularly when mechanical ventilatory support was required. In group 3 the relative risk of death increased to 6.2 when pretreatment transfusion exceeded 4 units of blood, to 7.3 when ulcer size was greater than 2 cm and to 4.2 when bilirubin level on admission exceeded 20 mmol/l (Table 5).

The nature of ulceration in group 3 was studied in detail (Table 6). The size and number of ulcers as well as the rebleeding and mortality rates were not statistically different with regard to the ulcer location. Of patients with ESRH, 12 had recurrent bleeding after treatment, six

Table 5 Factors associated with death in the three age groups by multivariate analysis

	Coefficient	P	Odds ratio
Group 1			
Concomitant medical illness	6.19	0.03	13.2 (1.2–24.7)
Mechanical ventilation	6.98	0.002	28.3 (1.6–50.9)
Complication	6.38	<0.0001	95.6 (38.3–140.3)
Group 2			
Total transfusion > 4 units	0.30	<0.0001	4.0 (2.0–7.7)
Complication	1.63	0.0001	17.9 (8.7–36.8)
Post-treatment rebleeding	11.12	0.006	5.1 (1.7–14.9)
Group 3			
Pretreatment transfusion > 4 units	2.06	<0.001	6.2 (2.3–16.7)
Ulcer size > 2 cm	0.42	<0.01	7.3 (2.8–18.9)
Haematemesis and melaena	1.22	<0.05	2.2 (0.72–6.8)
Admission bilirubin > 20 mmol/l*	0.06	<0.02	4.2 (3.3–21.6)

Values in parentheses are 95 per cent confidence intervals. *Normal range 7–19 mmol/l. Stepwise logistic regression

Table 6 Location, ulcer characteristics and treatment outcomes in group 3

	Ulcer location		
	Duodenal (n = 70)	Gastric (n = 99)	Duodenal + gastric (n = 36)
Rebleeding	15	30	7
Deaths	8	13	2
ESRH	27	47	36
Endoscopic treatment	4	15	24
Emergency surgery	4	3	10
Early elective surgery	5	15	0
No. of ulcers*	1.2(1.0)	1.4(0.9)	1.5(1.0)
Ulcer size (cm)*	1.9(2.1)	1.7(1.6)	1.6(1.5)

*Values are mean(s.d.). ESRH, endoscopic stigmata of recent haemorrhage. Mann-Whitney U test; Fisher's exact test; χ^2 test

after endoscopic therapy, three after emergency operation and three following early elective surgery. Thirteen patients died after treatment but there was no correlation between death and the type of treatment received; ten deaths were associated with treatment-related complications and only three were related to bleeding. It is particularly noteworthy that neither rebleeding nor death occurred if endoscopic therapy was performed early for 'at risk' patients at presentation. However, 11 of 52 patients (21 per cent) who rebled following admission experienced repeated bleeding after surgery ($P < 0.001$). Three continued to bleed and died. Patients with rebleeding were also more susceptible to the development of complications after treatment. The outcome was fatal in ten of 14 patients who developed complications, 11 of whom had experienced an episode of rebleeding ($P = 0.002$).

Discussion

Acute bleeding from peptic ulcer will usually stop spontaneously, irrespective of age, and there is no

evidence that the elderly have more severe bleeding at presentation than younger patients⁴. Massive bleeding in the elderly is, however, associated with a mortality rate of 50–70 per cent and conventional management has in the past, therefore, emphasized early operation to prevent rebleeding and death^{5,6}. The overall mortality rate for emergency surgery in the very old has fallen from 20 to 10 per cent over the past two decades, but for urgent gastroduodenal surgical intervention, this remains at 25–35 per cent, significantly higher than in younger individuals^{1,7,8}.

In a previous report⁹, immediate operation to control non-variceal gastrointestinal haemorrhage in patients aged over 50 years was not shown to confer any advantage over initial conservative management, and carried a mortality rate of 11.4 per cent which was not significantly different from the figure of 7.9 per cent documented in the conservative treatment group. This high mortality rate has been ascribed to co-morbid conditions, which are present in about 50 per cent of the very old¹⁰, and was 27.3 per cent for patients with associated medical illness but only 6.7 per cent for those without such an association⁹. With the development of successful endoscopic haemostatic techniques, more patients are being so treated in the hope that surgery and thus postoperative morbidity may be avoided. Although an initial haemostatic rate of over 90 per cent can be achieved, 10–19 per cent of patients will rebleed after treatment and many of these patients subsequently require operation^{11,12}.

In the present study, risk factors for rebleeding and death in the whole group of 1744 patients were in keeping with previously reported experience³. Rebleeding in this series was associated with a tenfold increase in mortality rate. When each of the selected age groups was studied separately, rebleeding was related to the severity of initial haemorrhage which was reflected by the number of units of blood transfused either before treatment or in total. Risk factors for death varied between the three groups. Patients aged less than 60 years were more likely to succumb if there was concomitant medical illness and if mechanical ventilatory support was required. The risk of death if complications arose after treatment was 96 times greater than when recovery was uneventful. Careful monitoring of patients at risk is required, with measures to prevent complications. Although hypotension should obviously be corrected to improve tissue perfusion, fluid overload, with the risk of pulmonary oedema, must be avoided.

Although treatment-related complications also constituted a risk factor for death in patients aged 60–79 years, the relative risk of death was only 17.9. The magnitude of initial bleeding also determined the final outcome in this group of patients. Severe bleeding with tachycardia and a need for continuous transfusion requires early intervention by endoscopic means or immediate operation.

In patients older than 80 years, the risk of death was increased in those with features of severe bleeding at presentation. Large ulcer size and impaired liver function were additional risk factors for death. Patients with such risk factors should be considered for initial endoscopic treatment and it is evident that gastric ulceration is associated with an increased need for intervention which is consistent with the observation of an increased risk of rebleeding when ulceration occurs in the stomach. Nevertheless, the time for complete healing of a large ulcer may be protracted, with the possibility of a rebleed occurring before ulceration is healed. Early operation, with excision

of the ulcer if possible, is an option after bleeding has been controlled endoscopically and the condition of the patient has improved. A patient with impaired liver function needs to be carefully assessed as to the advisability of early intervention to prevent ongoing bleeding and minimize the potential effects of massive transfusion in the presence of already compromised liver reserve. Such patients may tolerate operation poorly and every effort must be made to achieve successful haemostasis at therapeutic endoscopy.

When intervention is deemed necessary therapeutic endoscopy is the treatment of choice for very elderly patients and must be carried out before rebleeding occurs. There was no further bleeding or death if such treatment was given early but 21 per cent of patients who rebled developed further bleeding even after treatment for the rebleeding episode. The latter group of patients are also more susceptible to treatment-related complications and, as a result, a majority succumb.

Acknowledgements

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Surgical workshop

Avoiding pancreatic necrosis following pancreas-preserving D₃ lymphadenectomy for gastric cancer

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Pancreas-preserving lymphadenectomy for gastric cancer is a method of removing lymph nodes along the upper border of the pancreas without performing a distal pancreatic resection¹. The surgical technique includes ligation of the splenic artery at its origin and is effective in reducing the incidence of complications related to pancreatic resection, but carries the risk of pancreatic necrosis¹. A technique has been developed of pancreas-preserving D₃ lymphadenectomy for gastric cancer which reduces the risk of pancreatic necrosis.

Surgical technique

The surgical procedure involves dissection of the entire greater omentum, superior leaf of mesocolon and the serosa of the

pancreatic surface²; node dissection is then performed in the infraduodenal and supraduodenal areas, along the retropancreatic region (nodes n13 according to the Japanese Research Society for Gastric Cancer³), the hepatic pedicle (nodes n12), the mesenteric root (nodes n14) and along the common hepatic (nodes n8) and coeliac (nodes n9) arteries. The left gastric artery (nodes n7) is ligated at its origin and node dissection (nodes n11) is extended along the proximal third of the splenic artery, which is ligated distally approximately 5 cm from its origin. The spleen and distal pancreas are then mobilized and retracted. The tail of the pancreas is exposed carefully and the splenic vein and caudal pancreatic arteries are ligated and divided. Finally, the upper border of the pancreas is exposed and the spleen (nodes n10) and the middle and distal third of splenic artery with the surrounding fatty connective tissue and nodes (n11) are removed *en bloc*, together with the stomach, gastric omentum and perigastric nodes (n1–6). The pancreatic parenchyma and splenic vein are preserved.

Discussion

The dorsal pancreatic artery usually arises from the proximal third of the splenic artery^{4,5} and joins the posterosuperior pancreaticoduodenal artery (so-called Kirk arcade⁴) after giving off the transverse pancreatic artery. In the absence of the Kirk arcade (about 40 per cent of cases) the dorsal pancreatic artery is the sole blood supply to the left pancreas. Thus, ligation of the origin of the splenic artery exposes four in ten patients to the risk of pancreatic necrosis. The authors therefore preserve the proximal third of the splenic artery during pancreas-preserving lymphadenectomy by ligating the artery approximately 5 cm distal to its origin (*Fig. 1*).

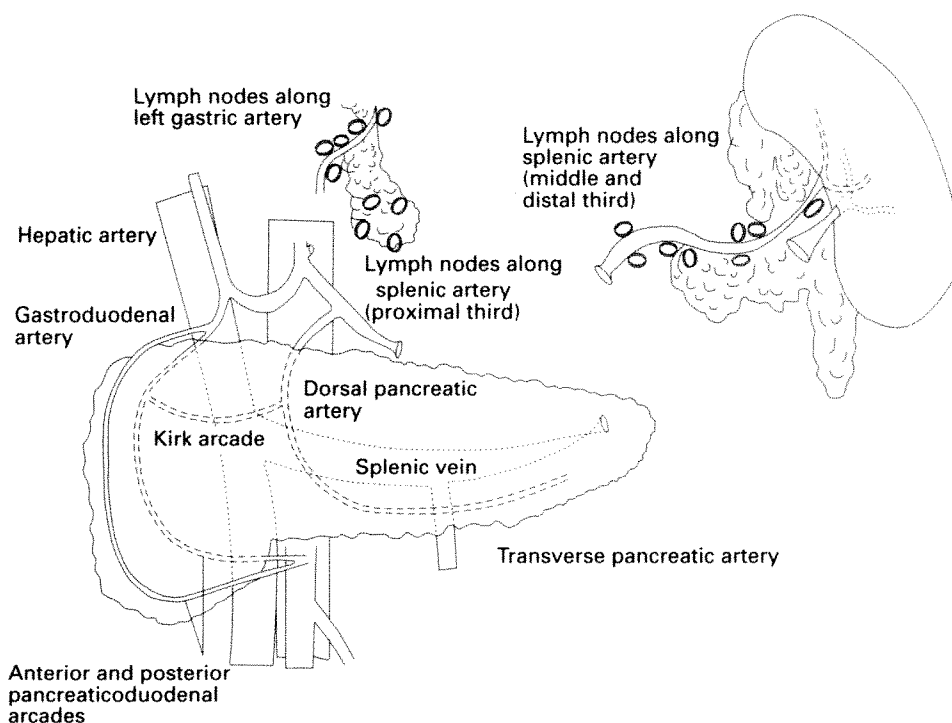


Fig. 1 Reported technique of pancreas-preserving D₃ lymphadenectomy. The splenic artery is ligated approximately 5 cm distal from its origin to preserve the blood supply to the left pancreas through the dorsal pancreatic artery

Using this technique on 180 consecutive patients (1981–1995), complications were rare: pancreatic necrosis, none; pancreatic fistula, one (0.6 per cent); and perioperative mortality, seven (3.9 per cent). The mean number of nodes retrieved was 44 (range 23–106). After curative resection ($n = 166$) the 5-year survival rate according to life-table analysis was 60 per cent (stage IA, 100 per cent; stage IB, 71 per cent; stage II, 67 per cent; stage IIIA, 39 per cent; and stage IIIB, 30 per cent).

This method of radical resection for gastric cancer does not appear to alter the potential cure rate but results in a low incidence of perioperative complications.

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In vivo assessment of the influence of cold preservation time on microvascular reperfusion injury after experimental small bowel transplantation

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Background This study describes the impact of prolonged cold storage on microvascular reperfusion injury of transplanted rat small bowel isografts.

Methods *In vivo* fluorescence microscopy was used to assess intestinal microcirculation after 6, 12, 18 and 24 h of cold (4°C) ischaemia in University of Wisconsin solution and 20–90 min of reperfusion. Sham-operated animals served as controls.

Results Whereas 6 and 12 h of ischaemia did not affect functional capillary density of the intestinal graft mucosa, villous perfusion was significantly impaired after 18 and 24 h of cold preservation. Similarly, microvascular perfusion of circular and longitudinal muscle was not affected after 6 h, but deteriorated following prolonged cold ischaemia. Leucocyte–endothelial cell interaction in submucosal venules was significantly enhanced after 6 h of ischaemia with peak values after 12 and 18 h. A progressive reduction of lymphatic capillary drainage indicated an ischaemia time-related deterioration in graft function.

Conclusion The results provide evidence that leucocyte–endothelial cell interaction in submucosal venules of the transplanted intestine is a primary step in the manifestation of reperfusion injury following short periods of cold ischaemia.

Small bowel transplantation has progressively improved with modern immunosuppressive strategies, which employ potent immunomodulators such as cyclosporin A, FK 506 and OKT 3¹. Another major problem hampering small bowel transplantation is ischaemia–reperfusion injury which is determined mainly by the quality of organ procurement². Early graft function and recipient survival largely depend on the duration of cold organ ischaemia^{3,4}. Besides threatening graft function and graft survival, microvascular reperfusion injury potentially contributes to the process of acute and chronic rejection^{5,6}.

The small bowel is uniquely susceptible to ischaemia–reperfusion injury with the microcirculation representing the primary target^{3,7}. This susceptibility is attributed to the high content of xanthine dehydrogenase within intestinal mucosa⁸. During ischaemia, xanthine dehydrogenase is converted to xanthine oxygenase, a major source of oxygen radicals generated in postischaemic tissues⁹. Oxidants produced early after the onset of reperfusion play an important role in promoting leucocyte adhesion associated with ischaemia–reperfusion⁸.

Reperfusion injury following short periods of normothermic ischaemia encompasses a variety of microvascular alterations characterized by capillary perfusion failure ('no reflow')¹⁰, accumulation, adherence and extravasation of leucocytes ('reflow paradox'), and loss of microvascular endothelial integrity¹¹. There is little information on the mechanisms underlying intestinal ischaemia–reperfusion injury, as related to the duration of cold preservation. The aim of the present study was to determine the severity of microvascular reperfusion injury in small bowel grafts according to the duration of cold ischaemia. The effects of different intervals of cold storage (6, 12, 18 and 24 h) on

capillary perfusion, leucocyte adherence and lymphatic capillary drainage in all layers of the intestinal wall were analysed by means of *in vivo* fluorescence microscopy¹².

Materials and methods

Animals

Heterotopic syngeneic small bowel transplantation was performed in adult male Lewis rats ($n = 30$; body-weight 170–250 g). The syngeneic model was chosen to exclude rejection-related effects. Both donors and recipients were fed with standard laboratory pellet food (Ssniff Spezialdiäten, Soest, Germany; 18000 IU/kg vitamin A, 1280 IU/kg vitamin D3, 120 mg/kg vitamin E) and water *ad libitum*. All experiments were performed in accordance with German legislation on protection of animals.

Microsurgical technique

After premedication with atropine (0.1 mg per kg body-weight subcutaneously) the animals were anaesthetized with ether. Fine polyethylene catheters (inner diameter 0.58 mm; Portex, Hythe, UK) were placed into the left jugular vein and carotid artery to record haemodynamic parameters continuously, inject fluorescent dyes and to substitute intravascular volume loss (3 ml/h Ringer's lactate intravenously; Perfusor V, B. Braun, Munich, Germany). Rectal temperature was monitored and maintained between 36.5 and 37.5°C by means of a heating pad. Small bowel was transplanted heterotopically using portaportal drainage and a non-suture cuff technique for the arterial anastomosis¹³. The preparation of the donor was carried out in principle as outlined by Monchik and Russell¹⁴. The abdomen of the donor animal was opened transversely. With the use of a Leitz dissecting microscope (Leitz, Wetzlar, Germany) the aorta was isolated from surrounding tissue at the origin of the superior mesenteric artery (SMA). The portal vein and superior mesenteric vein were separated from the pancreas by ligating all venous tributaries individually, including gastric and splenic veins. The distal

duodenum and the terminal ileum were divided and the organ was perfused with 20 ml chilled University of Wisconsin solution (UW, 4°C) via the SMA, applying a pressure¹⁵ of 50 cmH₂O. Penicillin G was added to the UW (200 000 units per 1000 ml) as recommended by Du Pont Pharma (Du Pont de Nemours, Bad Homburg, Germany). The small intestine was removed from the donor and the lumen was irrigated with 30 ml UW (4°C). The graft was finally stored at 4°C in UW for 6 h (group 2), 12 h (group 3), 18 h (group 4) and 24 h (group 5).

In the recipient animal the right renal artery and vein were freed from surrounding tissue. The renal vein was ligated and the renal artery was clamped near its aortic origin. The right kidney was removed after dissection of the ureter and minor vessels. For the anastomosis of the renal artery to the SMA, a cuff technique was used¹³. Briefly, a plastic cuff (Abbocath G24, inner diameter 0.7 mm; Abbott Ireland, Sligo, Ireland) was placed around the artery. The vessel was turned inside out over the cuff and fixed with a ligature. The SMA of the graft was pulled over the prepared cuff. Venous revascularization was accomplished by end-to-side anastomosis to the portal vein of the recipient using 9/0 running sutures (non-absorbable mononylon). Before reperfusion the preservation fluid, containing a high concentration of potassium, was flushed out with 15 ml cold Ringer's lactate (4°C) to prevent cardiac complications from hyperkalaemia upon reperfusion of the graft. By applying the non-suture cuff technique for arterial reanastomosis, mean(s.e.m.) time of cross-clamping the vena portae was 21.8(0.5) min. There was no significant difference in the duration of surgery between the groups.

In vivo microscopy

As already described in detail¹², 20 min after revascularization, a jejunal section of the transplanted bowel (approximately 6 cm from the upper end) was exteriorized on a specially designed mechanical stage attached to the microscope. The tissue was constantly superfused with Ringer's lactate at 37°C to avoid drying and local hypothermia, which might produce abnormal flow distribution¹⁶. *In vivo* microscopy was performed using a modified Leitz Orthoplan microscope with a 100-W HBO mercury lamp, attached to a Ploemo-Pak illuminator with I₂₃ and N₂ filter blocks (Leitz) for epi-illumination. With 10× (long distance) and 25× (water immersion) objectives, magnifications of 175× and 445× were achieved on the video screen (diagonal 33 cm). The intestinal microcirculation was visualized after intravenous administration of 0.2 ml 5 per cent fluorescein isothiocyanate (FITC)-labelled dextran (M_w 150 000; Sigma, St Louis, Missouri, USA) and 0.1 ml 0.2 per cent rhodamine-6G (M_w 479; Sigma). The microcirculation of the longitudinal and circular muscles as well as of the submucosa was assessed by varying the depth of focus of the microscope. To analyse mucosal microcirculation, a longitudinal incision (approximately 20 mm) along the antimesenteric border was performed using microcautery. In each transplant ten regions of interest were analysed to obtain representative values for every parameter. The pictures were recorded by means of a charge-coupled device video camera (FK 6990, Cohu Prospective Measurements, San Diego, California, USA) and transferred to a video recording system for off-line analysis ('U'-matic video tape recorder; Sony, Tokyo, Japan).

Microcirculatory evaluation

At low magnification the number of perfused villi (N_p) was determined to characterize overall mucosal perfusion and a mucosal perfusion rate (PR_m) was calculated by

$$PR_m (\%) = N_p / N_t$$

where N_t represents the total number of villi analysed. In addition, quantitative analysis of microhaemodynamics included the assessment of functional capillary density (FCD; length of red blood cell-perfused nutritive capillaries per area) and red blood cell velocity in mucosal, circular and longitudinal muscle capillaries¹². With FITC-dextran being drained by the subserosal

lymphatic capillary network, analysis of the density of perfused lymphatic microvessels (FC_LD) served as an indicator of graft function. FCD and FC_LD were assessed by computer-assisted image analysis (CAMAS Zeintl, Heidelberg, Germany)¹⁷. Red blood cell velocity in capillaries was measured applying frame-to-frame analysis.

With the use of the fluorescent marker rhodamine-6G leucocytes were stained *in vivo* and classified according to their interaction with the venular endothelium as rolling, adherent or non-adherent cells. In submucosal postcapillary venules (PVs) and intramural collecting venules (CVs) leucocytes adhering to the endothelium were determined in each vessel segment as cells that did not move or detach from the endothelial lining during 30 s of observation; adherent cells were recorded as the number of cells per mm² endothelial surface as calculated from diameter and length of the vessel segment studied, assuming cylindrical geometry¹¹. Rolling leucocytes were defined as white blood cells moving at a velocity less than two-fifths that of red blood cells in the centre line of the microvessel^{11,17} and were quantified as percentage of non-adherent leucocytes passing through the observed vessel within 30 s of observation.

Histology

Tissue samples were taken at the end of each experiment (90 min after onset of reperfusion). The samples were fixed immediately in 10 per cent neutral buffered formalin. The tissues were dehydrated, embedded in paraffin, cut at approximately 3 µm (Microtome; Leica, Munich, Germany) and stained with haematoxylin and eosin. Coded histopathological sections were examined for inflammation and necrosis of villus and crypt epithelial cells and destruction of the villus architecture as induced by ischaemia-reperfusion^{18,19}.

Electron microscopy

After intravital microscopy, several grafts from each group were perfused with Karnovsky solution (25 ml paraformaldehyde 8 per cent, 10 ml glutaraldehyde 25 per cent, 15 ml Sörensen buffer) via a polyethylene catheter inserted into the abdominal aorta (perfusion pressure 50 cmH₂O). Specimens were cut into small blocks and subjected to further fixation with 2 per cent osmium tetroxide in Sörensen buffer (pH 7.4) at room temperature for 2 h. Subsequently, the tissue was dehydrated, embedded in Epon monomer solution (Serva, Heidelberg, Germany) at 6°C for 24 h, cut with a diamond knife (Reichert and Jung Ultramicrotome; Munich, Germany), stained with uranyl acetate and lead citrate, and finally examined with the use of a transmission electron microscope (HU-12 AS; Hitachi, Tokyo, Japan) with 80 kV acceleration voltage.

Experimental protocol

In six animals from each group heterotopic syngeneic small bowel transplantation was performed after 6 h (group 2), 12 h (group 3), 18 h (group 4) and 24 h (group 5) of cold storage of the graft in UW (4°C). Mean arterial pressure (MAP) and heart rate were recorded continuously during the entire surgical and *in vivo* microscopic procedure. Arterial blood gases were assessed during surgery and at the end of the experiment. Peripheral blood cell count was determined 90 min after revascularization with the use of a Coulter Counter T 540 (Coulter Electronics, Hialeah, Florida, USA). *In vivo* microscopy was performed for 20–90 min after reperfusion. Six animals without transplantation were subjected to an identical protocol of intravital microscopy and served as sham-operated controls (group 1). After completion of intravital microscopy, animals were sacrificed by exsanguination for collection of blood and tissue samples.

Statistical analysis

All values are presented as mean(s.e.m.). Data were evaluated by one-way analysis of variance (ANOVA) and Student–Newman–Keuls test. If data failed to pass a normality test, Kruskal–Wallis

one-way ANOVA on ranks and Dunn's post hoc test were performed. $P < 0.05$ was considered to be statistically significant.

Results

In sham-operated animals no significant alteration of haemodynamic parameters was observed during the course of the experiment (baseline MAP 88.3(3.0) versus 85.7(4.2) mmHg at the end of the experiment). The MAP of animals subjected to heterotopic isogeneic small bowel transplantation was reduced at the time of completion of surgery compared with that in sham-operated controls. However, no significant difference was demonstrated 15 min after the onset of reperfusion or at the end of the experiment. In contrast, in rats whose grafts had 24 h of cold storage (group 5) no recovery was observed during the course of the experiment and additional volume substitution was required to maintain MAP above 60 mmHg. Arterial partial pressure of oxygen and peripheral blood cell count was not significantly different between the groups, either at baseline or at the end of the experiment.

Intestinal microcirculation in sham-operated animals

Investigation of the intestinal microcirculation of sham-operated animals revealed homogeneous perfusion of both the mucosal and muscle capillary network. Values of FCD and red blood cell velocity in muscle were significantly lower than those in the mucosal layer (Table 1). Some 26 and 12 per cent of non-adherent leucocytes were seen rolling along the endothelial lining of submucosal PVs and intramural CVs respectively. Firm attachment of leucocytes was rarely observed (Fig. 1).

The architecture of lymphatics in the intestinal subserosa was a network of microvessels, coalescing into larger draining lymphatic ducts^{12,20}. With values of approximately 36 per cm, FC_D was significantly lower than the FCD of capillary blood vessels in mucosa and muscle layers ($P < 0.05$).

All sham-operated controls showed intestinal motility on macroscopic inspection.

Microcirculation of small bowel isografts

Mucosa. Following 6 h of cold preservation, there was no difference in PR_m, mucosal FCD and red blood cell

velocity in villous capillaries compared with sham-operated controls. However, a significant reduction of PR_m and capillary red blood cell velocity ($P < 0.05$) was observed after 12 h of cold ischaemia. After prolonged cold storage of 18 h, deterioration of PR_m was associated with a significant decrease in mucosal FCD compared with sham-operated controls ($P < 0.05$). Reperfusion injury was most pronounced after 24 h of cold ischaemia; only 40 per cent of the intestinal villi were reperfused, producing minimum values of mucosal FCD and capillary red blood cell velocity (Table 1). Haemorrhage from villous capillaries was observed frequently.

Muscle. Analysis of FCD within intestinal muscle layers revealed no significant alterations after 6 h of cold preservation; in contrast, 12 h of ischaemia was associated with a significant reduction of FCD in the circular muscle layer compared with controls. Prolonged preservation of 18 h and, especially, 24 h further aggravated microvascular reperfusion failure within both longitudinal and circular muscle layers (Table 1). In parallel, red blood cell velocity was reduced within all groups, decreasing with prolongation of cold ischaemia time (Table 1).

Submucosa. In contrast to microvascular perfusion within mucosa and muscle which was not altered, 6 h of cold ischaemia significantly enhanced leucocyte-endothelial cell interaction with a fourfold increase in the number of firmly adherent white blood cells in submucosal PVs compared with sham-operated controls. After 12 h and 18 h of cold preservation, primary and secondary leucocyte-endothelial cell interaction was further enhanced, as indicated by peak numbers of leucocytes rolling along the endothelial lining and firmly adhering in PVs and CVs ($P < 0.05$) (Figs 1 and 2). No further induction, but rather a decrease in leucocyte adherence was demonstrated following 24 h of cold preservation compared with values obtained in groups 3 and 4.

Subserosa. Both microvascular reperfusion failure and leucocyte-endothelial cell interaction were associated with a marked decrease of FC_D in the intestinal subserosa. The number of perfused lymphatic capillaries was found to decrease as the duration of ischaemia increased (Table 1).

Table 1 Microhaemodynamic parameters after small bowel transplantation

	Sham operated (group 1)	Cold preservation time before transplantation (h)			
		6 (group 2)	12 (group 3)	18 (group 4)	24 (group 5)
Mucosa					
Perfusion rate (%)	100	99.8(0.2)	89.7(4.1)*	87.9(8.8)	40.2(21.2)*
Functional capillary density (per cm)	465.1(18.1)	409.3(14.0)	340.3(13.6)	301.3(23.1)*	94.7(40.2)*†
Capillary RBC velocity (mm/s)	0.90(0.06)	0.75(0.09)	0.52(0.03)*†	0.48(0.04)*†	0.42(0.06)*†
Circular muscle					
Functional capillary density (per cm)	281.1(14.9)	273.4(17.0)	174.8(29.4)*†	81.4(13.5)*†‡	62.4(26.4)*†‡
Capillary RBC velocity (mm/s)	1.12(0.17)	0.67(0.04)*	0.60(0.05)*	0.53(0.04)*	0.52(0.05)*
Longitudinal muscle					
Functional capillary density (per cm)	179.6(11.1)	153.9(3.4)	142.1(5.6)	88.7(7.6)*†‡	65.7(20.2)*†‡
Capillary RBC velocity (mm/s)	1.15(0.12)	0.70(0.03)*	0.61(0.06)*	0.51(0.04)*	0.49(0.04)*
Subserosa					
Lymphatic capillary density (per cm)	35.9(2.7)	15.8(3.9)*	12.2(1.8)*	6.4(2.7)*	4.7(3.4)*

Values are mean(s.e.m.) ($n = 6$ per group). RBC, red blood cell. * $P < 0.05$ versus group 1; † $P < 0.05$ versus group 2; ‡ $P < 0.05$ versus group 3 (one-way analysis of variance and Student–Newman–Keuls test)

Intestinal motility was noted in all animals; however, in group 5 peristalsis was demonstrated only with the use of the microscope.

Histology

The intestine of sham-operated animals was found to be normal without signs of mucosal or muscle layer injury. No sloughing of the apical villous epithelium and only mild oedema in the lamina propria were observed after 6 h of cold ischaemia and reperfusion. Prolonged cold

storage was associated with separation of the epithelium from the lamina propria, involving the entire villi (group 3); significant damage extending to the level of the crypts was prominent in group 4. Severe mucosal injury was regularly found after 24 h of cold preservation and reperfusion (group 5), as characterized by haemorrhage and loss of villous epithelium leaving the lamina propria completely denuded.

Electron microscopy

Sham-operated controls had normal ultrastructure of small intestinal muscle, submucosa and mucosa with microvilli on the apical pole of the enterocytes. After cold storage and reperfusion, enterocytes lost their characteristic arrangement, showing shortened or absent microvilli and disintegration of the mitochondria (Fig. 3a). After 24 h of preservation the epithelium was detached, exposing the lamina propria (Fig. 3b). Erythrocyte and platelet sludging in capillaries was seen frequently after prolonged cold ischaemia. However, swelling of capillary endothelial cells was not observed. Intimate association

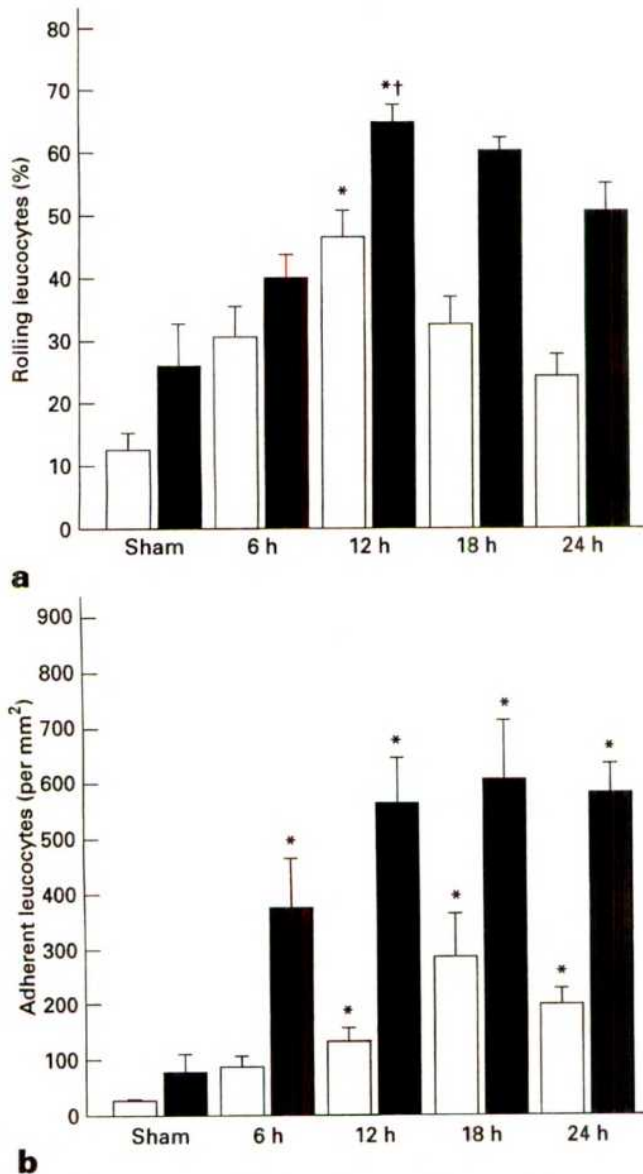


Fig. 1 Leucocyte-endothelial cell interaction in submucosal postcapillary venules (■) and intramural collecting venules (□) of sham-operated controls ($n = 6$) and animals that underwent heterotopic transplantation of intestinal isografts, subjected to 6, 12, 18 and 24 h of cold preservation and reperfusion ($n = 6$ per group). **a** Percentage of rolling leucocytes and **b** number of adherent leucocytes per mm^2 endothelial surface. Values are mean (s.e.m.). * $P < 0.05$ versus sham; † $P < 0.05$ versus 6 h of cold preservation (Kruskal-Wallis one-way analysis of variance on ranks and Dunn's post hoc test)

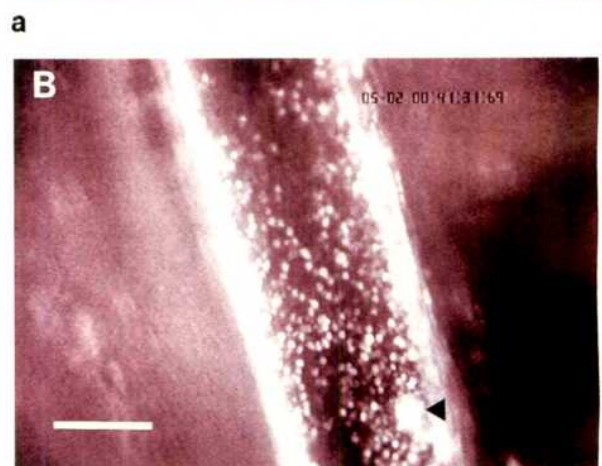
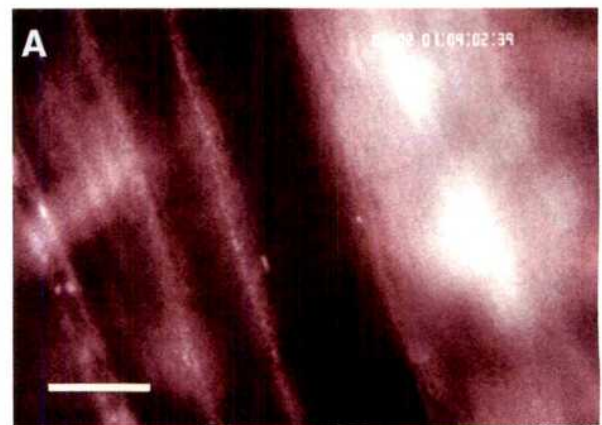


Fig. 2 **a** Submucosal collecting venule of a sham-operated control animal (group 1), visualized by *in vivo* fluorescence microscopy and contrast enhancement with rhodamine-6G; only a few leucocytes adhere to the endothelium. **b** After 18 h of cold storage accumulation of rhodamine-stained leucocytes is enhanced. Note the large number of leucocytes adherent to the endothelial lining which may in some instances result in aggregation of platelets and white blood cells (arrowhead). Original magnification $\times 445$

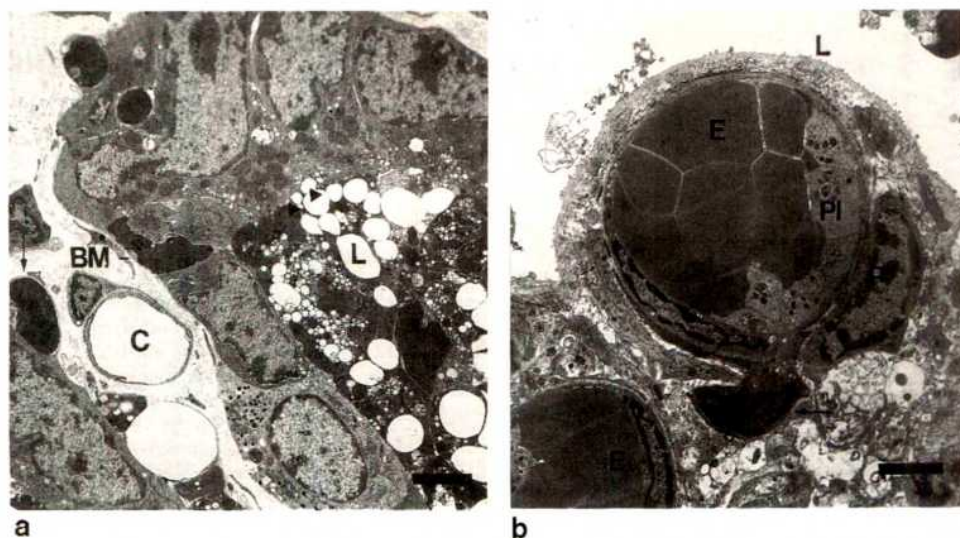


Fig. 3 Electron micrographs of intestinal mucosa. **a** After 18 h of cold ischaemia and 90 min of reperfusion the epithelium appears flattened. Note the absence of microvilli and the presence of fluid between intercellular membranes. The mitochondria are swollen with destruction of cristae (arrowheads). Underneath the basement membrane (BM) there is capillary obstruction by red blood cells (arrow). Original magnification $\times 3000$. **b** After 24 h of cold storage and reperfusion the denuded mucosa with lamina propria is exposed. Note the dilated capillaries obstructed by platelets (PI) and red blood cells (E). A granulocyte leaves the microvessel (arrow). C, capillary; L, gut lumen; P, pericyte. Original magnification $\times 4400$.

between neutrophils and the venular endothelial cell was a prominent phenomenon following 12, 18 and 24 h of cold preservation. Neutrophil pseudopodia were seen to extend between endothelial cell processes suggesting granulocyte diapedesis and emigration (Fig. 3b).

Discussion

Small bowel transplantation has been advocated for patients with short bowel syndrome for whom long-term parenteral nutrition is not a viable option. Whereas considerable research has focused on the development of new immunosuppressive agents, little is known about the early microcirculatory alterations associated with reperfusion and reoxygenation of intestinal grafts²¹. The present study was performed to determine the nature and magnitude of microvascular reperfusion injury in small bowel grafts with respect to cold ischaemia time. The use of intravital microscopy employing different fluorescent dyes allowed for the simultaneous quantitative analysis of a variety of parameters from the intestinal microcirculation¹².

Reperfusion of the ischaemic intestine resulted in an injury response associated with inflammatory cell infiltration and microvascular perfusion failure. After 1 h or 6 h of cold intestinal ischaemia with storage in UW, no significant capillary perfusion failure could be identified⁴. However, enhanced leucocyte-endothelial cell interaction was demonstrated, indicating that leucocyte adherence is a primary step in the pathophysiological sequelae following cold ischaemia-reperfusion. Peak values of primary ('leucocyte rolling') and secondary ('leucocyte sticking') leucocyte-endothelium interaction in PVs and CVs of the submucosa were observed after 12 and 18 h of cold preservation. As verified by electron microscopy, neutrophils were the predominant leucocytes adhering to the venular wall during initial reperfusion.

The multistep process of leucocyte-endothelial cell interaction requires activation and attraction of leucocytes by potent inflammatory mediators (oxygen radicals, leukotriene B₄ and platelet activating factor)²² and may involve several adhesion complexes (integrins, selectins and intercellular adhesion molecules) expressed on the surface either of endothelial cells or neutrophils²³. Although the molecular determinants of leucocyte-endothelial cell interaction following cold intestinal preservation-reperfusion are poorly understood, a role for the neutrophil adhesion molecule CD11/CD18 has been demonstrated recently²¹.

Besides leucocyte accumulation in PVs, capillary perfusion failure ('no reflow') in the muscle and mucosal layers was prominent after prolonged cold intestinal ischaemia of 12, 18 and 24 h. Several mechanisms may be involved. There is evidence that endothelial cell swelling contributes to the manifestation of no reflow following warm ischaemia-reperfusion¹⁰. Swelling of capillary endothelium could not be demonstrated in this study following cold storage-reperfusion of the small intestine. In contrast, capillary obstruction by erythrocytes and thrombocytes was frequently observed, indicating that microvascular platelet and red blood cell aggregation plays a crucial role in the manifestation of postischaemic no reflow. Reperfusion of intestinal isografts is associated with an ischaemia time-dependent increase in intestinal microvascular permeability and endothelial cell injury^{3,21}. Endothelial cell dysfunction, which might partly be mediated by activated neutrophils²⁴, enhances extravasation of fluid to the extracellular space. Consequently, an increase in capillary microvascular haematocrit impairs microvascular blood fluidity, thus facilitating capillary obstruction by platelet and erythrocyte aggregates²⁵. The reduction of red cell flow velocity in mucosa and the muscle capillary network seen after prolonged intestinal preservation suggests that low capillary shear rates may play a role in microvascular reperfusion failure.

Subserosal lymphatic capillary density was used to assess intestinal graft function. Enhancement of leucocyte-endothelium interaction following 1 and 6 h of cold ischaemia was paralleled by a reduction of subserosal lymphatic capillary drainage. This agrees with recent reports which indicate that intestinal lymph flow and lymphatic lipid output are highly susceptible to normothermic and hypothermic ischaemia-reperfusion^{26,27}. The exact pathomechanisms underlying the ischaemia time-dependent impairment of FC_LD are poorly understood although the present study provides evidence for a causative role of adherent leucocytes. Similarly, recent observations suggest that activated and adherent leucocytes are the primary mediators of normothermic ischaemia-reperfusion-induced lymphatic dysfunction, since animals rendered neutropenic do not exhibit impairment of lymphatic lipid transport⁷.

Only moderate ultrastructural alterations of the mucosal epithelium were observed following 6 h of cold ischaemia; however, a progradient separation of the epithelium from the lamina propria became apparent with increasing duration of preservation. Because leucocyte adhesion was associated with mucosal ischaemia-reperfusion damage, a causative role of leucocyte adhesion in the pathogenesis of mucosal reperfusion injury can be assumed.

It was found that the extent of no reflow corresponds with the degree of damage, indicating that impaired nutritional perfusion may play a crucial part in the development of postischaemic epithelial cell damage. This agrees with recent observations that cold ischaemia injury of the small bowel primarily involves the microvasculature of the mucosa and secondarily proceeds towards global mucosal damage³. Preservation of intestinal microcirculation seems to be imperative since a number of postoperative complications such as bacterial translocation may arise from mucosal barrier dysfunction and early mucosal integrity correlates with postoperative outcome¹.

In conclusion, progressive capillary perfusion failure was documented following prolonged ischaemia. In contrast, an increase in leucocyte-endothelial cell interaction was demonstrated even after brief periods of ischaemia. This inflammatory cell infiltration was associated with a significant reduction of subserosal lymphatic drainage and with severe impairment of epithelial cell integrity, indicating early graft dysfunction. New therapeutic strategies will have to encompass the protection of postischaemic intestinal microcirculation during initial graft reperfusion, including prevention of leucocyte adherence and preservation of adequate nutritive perfusion.

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Assessment of combined bile acid and pH profiles using an automated sampling device in gastro-oesophageal reflux disease

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Background Bile acid reflux is an important component of duodenogastro-oesophageal reflux but there is no effective method of quantifying it. The contribution of bile acids to oesophageal pH is unknown.

Methods Oesophageal aspirates were collected over 15 h using a new automated suction device and pH was monitored in ten asymptomatic volunteers (group 1) and 30 patients with reflux oesophagitis (group 2, minimal mucosal injury; group 3, erosive oesophagitis; group 4, stricture or Barrett's oesophagus). Bile acid assay was performed by high-performance liquid chromatography.

Results The concentration of bile acids was significantly higher in group 3 (median (interquartile range) 124 (50–301) $\mu\text{mol/l}$) and group 4 (181 (85–591) $\mu\text{mol/l}$) compared with group 1 (0 $\mu\text{mol/l}$) and group 2 (14 (0–100) $\mu\text{mol/l}$). Patients in groups 3 and 4 also had significantly greater DeMeester acid scores. Combined bile acid and oesophageal acid reflux was observed in eight of ten patients with stricture or Barrett's oesophagus. There was no correlation between total bile acid concentration and oesophageal acid or alkaline exposure.

Conclusion This study supports the theory of toxic synergism between acid and bile acids in reflux oesophagitis. Bile acids may contribute to the pathogenesis of Barrett's metaplasia.

Gastric acid is known to be involved in the aetiology of reflux oesophagitis but the contribution of bile acids is unknown and attention has switched to quantification of duodenogastro-oesophageal reflux. The evidence, mostly from oesophageal perfusion studies in animal models, supports injury by bile acids^{1,2} although pepsin³ and trypsin^{4,5} have also been implicated. In humans the evidence that bile acids are detrimental to the oesophageal mucosa has been mostly indirect, relying either on the documentation of simultaneous 'alkaline' reflux on combined gastric and oesophageal pH monitoring^{6–8} or monitoring of bilirubin with the spectrophotometric probe 'Bilitec' (Synectic Medical, Irvine, Texas, USA)^{9,10}. Direct aspiration^{11–15} has been performed to determine the bile acid content of the oesophageal refluxate, but results are conflicting because of the variable periods of study and analysis of pooled samples. A new technique of combined oesophageal sampling and pH monitoring is presented using a purpose-built automated aspiration device. Bile acid estimations were performed in patients with varying grades of oesophagitis and results correlated with simultaneously measured oesophageal pH.

Patients and methods

Oesophageal sampling studies were performed in ten asymptomatic volunteers (M:F ratio 4:1; median age 28.5 (range 19–50) years) and 30 patients with symptoms of gastro-oesophageal reflux (M:F ratio 2:1; median age 58.5 (range 27–79) years) and endoscopic evidence of oesophagitis. All subjects gave written informed consent for the study which was approved by the local ethics committee. The volunteers (group 1) were not subjected to upper gastrointestinal endoscopy. The

patient groups (ten patients each) were classified according to the endoscopic findings: group 2, no mucosal injury or erythema; group 3, erosive oesophagitis; group 4, oesophageal stricture or Barrett's oesophagus. All acid suppression and prokinetic medication was stopped at least 1 week before study. Patients in group 4 had any stricture dilated a minimum of 6 weeks before the investigation. The study was performed as an inpatient procedure over 15 h between 18.00 and 09.00 hours. A 14-Fr double-lumen sump tube incorporating an antimony pH electrode (Zinetics Medical, Salt Lake City, Utah, USA) was passed nasally and the tip positioned 5 cm above the manometrically located lower oesophageal sphincter. A period of 2 h was allowed for the effects of intubation to subside before attaching the end of the sump tube to the suction channel of the new device. The design and development of this device has been published elsewhere¹⁶. The main objective in designing the sampling device was to incorporate an automated suction mechanism to aspirate fluid from the distal oesophagus continuously. The retrieval time of each sample was logged into the memory of a microprocessor within the device. The oesophageal aspirates were collected in autoanalyser cups (capacity 1.6 ml) and stored at -20°C for bile acid assay using high-performance liquid chromatography (HPLC). Oesophageal pH was simultaneously monitored with the Flexilog (Oakfield Instruments, Oxford, UK) solid-state digital recorder. The subjects were allowed to drink fluids throughout the procedure.

High-performance liquid chromatography

Reversed-phase HPLC was used for the bile acid assay. This method was modified using a post-column derivation step; the bile acids were separated by the chromatography but the individual bile acids were then reacted with the enzyme 3- α hydroxy steroid dehydrogenase (3- α HSD) using nicotinamide adenine dinucleotide as cofactor. The end product of this post-column reaction was the reduced form of nicotinamide adenine dinucleotide which was measured fluorometrically to quantify the bile acids. The analytical column (stationary phase) was a single Spherisorb (Waters, Milford, Massachusetts, USA) S5 ODS2 column (250 $\times$ 4.6 mm internal diameter) with a porous, spherical silica-based packing. The oesophageal aliquots were allowed to thaw at room temperature and the volume of each noted. Each aspirate was separated from mucus and particulate

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material by centrifugation at 4000 r.p.m. for 5 min. The bile acids from the oesophageal sample were extracted using clean-up extraction tubes (C18 Octadecyl (Technical, Stockport, UK) endcapped) with methanol as the solvent. A 20- μ l sample was injected into a high-pressure mobile phase (9 per cent v/v methanol, 90 per cent v/v phosphate buffer and 1 per cent v/v tetrahydrofuran; pH adjusted to pH 3.5 with orthophosphoric acid). The elution time per sample was 35 min with clear separation of 14 bile acid fractions.

Statistical analysis

The total bile acid concentration data were not normally distributed. A combination of two non-parametric tests, the Kruskal-Wallis and Mann-Whitney *U* tests (six in number), was used to compare the bile acid levels in the four groups. The prevalence of bile acid-positive samples and those with high concentration (greater than 200 μ mol/l) was compared using the χ^2 or Fisher's exact test. Correlation between bile acid concentration and oesophageal pH was done using Spearman rank order correlations.

Results

Oesophageal aspiration studies of 15 h duration were performed successfully on 40 subjects. In two cases the tests were repeated because of mechanical failure of the sampling device. Some 2244 individual samples were obtained for bile acid analysis. The results of the bile acid assay and pH profile are shown in Table 1. The volume of aspirate ranged from 20 to 113 ml with a mean of 46 ml per subject. There were no significant differences in the total volume of aspirate obtained in each group. Bile acids were detected in over a third of the samples from patients with severe oesophageal mucosal damage (groups 3 and 4). Patients with minimal or no oesophageal mucosal injury had fewer than one-tenth of the total samples testing positive for bile acids while the control group had negligible acid reflux. There was a significant difference in the total bile acid concentration in samples from the four groups ($P < 0.001$, Kruskal-Wallis test) with the highest concentrations in patients with endoscopic evidence of severe mucosal injury (groups 3 and 4).

There was a progressive increase in oesophageal acid exposure, expressed as percentage of the total time pH was less than 4, from groups 1 to 4 but only the patients in group 4 had significantly greater acid exposure (Fig. 1). When DeMeester's composite acid scores were compared, significantly higher scores were obtained in groups 3 and

4. Oesophageal alkaline exposure time, defined as the percentage of the total time when pH was greater than 7, was unrelated to the grade of disease in the different groups. In most instances the individual profiles showed that bile acids refluxed concurrently with gastric acid. Overall, there was no correlation between the total bile acid concentration and oesophageal acid exposure ($r_s = 0.3$) or alkaline exposure ($r_s = 0.3$).

The patients were classified further according to reflux patterns into predominantly acid refluxers (more than 6 per cent of total time at pH less than 4), bile acid refluxers (peak concentrations greater than 100 μ mol/l), and mixed acid and bile acid refluxers. Patients with oesophageal injury had an increased prevalence of mixed reflux (four of ten in the erosive oesophagitis group and eight of ten in the stricture/Barrett's oesophagus group *versus* one of ten in the minimal injury group and none in the controls). Six patients (two in each patient group) were found to have significant bile acid reflux in the absence of an increased acid exposure. Two subjects in the control group, although asymptomatic, had increased acid exposure.

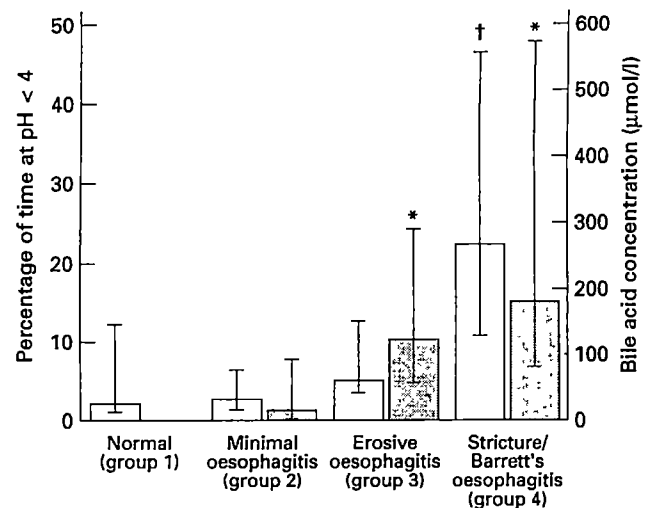


Fig. 1 Oesophageal bile acid concentrations (□) compared with acid exposure (pH < 4) (□) in the four groups. Values are median (interquartile range). * $P < 0.05$ versus groups 1 and 2; † $P < 0.05$ versus groups 1–3 (Mann-Whitney *U* test)

Table 1 Results of the oesophageal pH and bile acid assay

	Group 1 normal (n = 10)	Group 2 minimal oesophagitis (n = 10)	Group 3 erosive oesophagitis (n = 10)	Group 4 stricture/ Barrett's oesophagus (n = 10)
No. of samples	516	905	457	366
Volume of aspirate (ml per 15 h)	407	686	351	415
Patients with oesophageal reflux	2	5	8	10
Percentage of samples positive for bile acid	2.3	8.7	34.4†	68.0†
Percentage of samples with >200 μ mol/l bile acid	0	4.0	7.2	29.2‡
Peak bile acid (μ mol/l)*	0 (0–0)	14 (0–100)§	124 (50–301)†	181 (85–591)†
Percentage of total time pH < 4*	2.1 (0.9–12.1)	2.7 (1.3–5.9)	5.1 (3.6–12.1)	22.3 (10.0–46.0)‡
Percentage of total time pH > 7*	6.8 (2.4–23.6)	10.9 (2.1–17.6)	4.1 (0.2–12.3)	14.3 (5.9–15.8)

*Values are median (interquartile range). † $P < 0.05$ versus groups 1 and 2; ‡ $P < 0.05$ versus groups 1–3; § $P < 0.05$ versus group 1

Discussion

Acid reflux alone may not be sufficient to account for the development of complications in gastro-oesophageal reflux disease. Measuring the non-acid constituents of reflux is not as straightforward as pH monitoring but oesophageal sampling by direct aspiration can determine accurately the composition of the refluxate. Several sampling studies have demonstrated, with variable results, the presence of bile acids in patients with reflux oesophagitis^{11–15}. The major drawback of these studies is that the authors have relied on analysis of pooled samples. Oesophageal bile acid concentration varied from zero to greater than 10 000 $\mu\text{mol/l}$ in aspiration studies by Gotley *et al.*¹¹ and Iftikhar *et al.*¹² who analysed 2-h pooled samples over a 16-h interval, while Stein *et al.*¹³ using a longer interval of 3 and 8 h measured peak concentrations of only 107.7 $\mu\text{mol/l}$. This demonstrates a 'dilution' effect and a likelihood of missing brief reflux episodes with potentially harmful concentrations of bile acids. Using a new technique of timed oesophageal aspiration the present authors have been able to improve the accuracy of sampling and demonstrate the temporal relationship between bile acid reflux and oesophageal pH. Individual patient profiles showed that episodes of bile reflux occurred over a wide pH range (between 2 and 8), but in most instances bile reflux was associated with acid reflux.

Documentation of 'alkaline' reflux on dual gastric and oesophageal pH monitoring has often been interpreted as evidence of duodenal 'bile' reflux^{6–8,13}. No such relationship was seen in the present study. On the contrary, the group with the highest levels of bile acids in the refluxate, the stricture/Barrett's group, also had maximum acid exposure. This, however, did not translate statistically into a significant correlation.

This study suggests that there is an association between bile acid reflux and severity of oesophageal mucosal injury. Bile acids were detected in 18 of 20 patients with severe mucosal damage (grade 2–4, Savary-Miller) and, significantly, in higher concentrations. Concentrations of bile acids greater than 200 $\mu\text{mol/l}$ have been shown to cause mucosal barrier disruption^{17,18}. Although a progressive increase in oesophageal acid exposure and bile acid concentration was noted with advancing grade of reflux disease, the increments were not proportionate. Patients with erosive oesophagitis (group 3) had an almost tenfold increase in the oesophageal bile acid concentration compared with patients with minimal mucosal injury (group 2), but there was no significant difference in the acid exposure. In the presence of acid, bile acids may enhance mucosal damage. None of the less than four patients with endoscopic evidence of severe mucosal injury had predominantly bile acid reflux. This also implies that monitoring either component of the refluxate is not representative of the magnitude of reflux overall.

There is a tendency towards a higher frequency and duration of duodenogastro-oesophageal reflux in Barrett's oesophagitis^{8,19–21}. One-third of the samples in patients with stricture or Barrett's oesophagus had bile acid concentrations in excess of 200 $\mu\text{mol/l}$, significantly greater than in the patients with erosive oesophagitis. Similar findings have been reported by Iftikhar *et al.*¹² and Stein *et al.*¹³. Studies with the 'Bilitec' probe, designed to monitor reflux of bilirubin, have also shown an increase in bile reflux in Barrett's oesophagus^{22,23}. This was associated with increased acid exposure, reinforcing the concept of acid and bile synergism in reflux oesophagitis²⁴. There was

no correlation between bile and alkaline reflux^{25,26}. Although the 'Bilitec' method of bile monitoring has the advantage of being ambulatory, it has limitations. At pH less than 3.5 it underestimates bilirubin by at least 30 per cent²³ and certain diets⁹ or the tendency of the refluxate to 'stick' to the probe tip interfere with the detection system.

This study has shown that bile acids may be an important contributing factor in the aetiology of reflux oesophagitis and that the absence of acid reflux does not exclude a high bile acid content in the refluxate. This method of investigation has the potential to identify patients with toxic components in their refluxate who could be offered surgery to avoid complications.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Tumour necrosis factor and inflammatory bowel disease

Sir

Mr Armstrong and colleagues reviewed carefully the current evidence regarding the role played by tumour necrosis factor (TNF) α in the aetiology of inflammatory bowel disease (IBD) (*Br J Surg* 1997; 84: 1051–8). TNF is a proinflammatory cytokine and appears to be a fundamental mediator of the changes seen in IBD with evidence of benefit by anti-TNF treatment. A future course of research should evolve from the finding that production of TNF is under polymorphic genetic control¹. Patients tend to be either low or high TNF secretors to any given stimulus depending on their inherited allele. Thus, TNF genotype may have a profound effect on the relapsing course of IBD or on the aetiology of the disease. Interleukin (IL)10 is an anti-inflammatory cytokine with inhibitory qualities including TNF suppression². IL-10 is also raised in IBD^{3,4} and, like TNF, is under polymorphic genetic control⁵. High TNF and/or low IL-10 may confer a poor prognosis and, likewise, low TNF and/or high IL-10 may improve the prognosis. These findings may also have important applications in the development of new treatment.

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- 1 Wilson AG, Symons JA, McDowell TL, Di Giovine FS, Duff GW. Effects of a tumour necrosis factor (TNF α) promoter base transition on transcriptional activity. *Br J Rheumatol* 1994; 33(Suppl 1): 89 (Abstract).
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Laparoscopic approach to pelvic congestion syndrome

Sir

The authors report relief of symptoms in one of two patients by laparoscopic cutting of the ovarian vein in this syndrome (*Br J Surg* 1997; 84: 1264), which has been described by Hobbs. Hobbs, I believe, ascribed the condition to pelvic venous congestion secondary to previous undiagnosed internal iliac vein thrombosis where the ovarian and vulval veins are acting as collaterals, and postulated that the symptoms of pain associated with menstruation and intercourse reflected even higher venous pressure at times of pelvic congestion. Should his hypothesis be correct, surely interruption of the dilated ovarian vein would exacerbate rather than improve the condition? I suggest, therefore, that these highly preliminary results should be interpreted with great caution, particularly as in both cases the ovarian vein ligation was combined with an operation to control the varicose veins.

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- 1 Hobbs JT. The pelvic congestion syndrome. *Br J Hosp Med* 1990; 43: 200–6.

Authors' reply

Sir

We are surprised by Mr Jamieson's comments as Hobbs¹ states clearly that retrograde flow in the ovarian veins was the primary problem.

While undiagnosed internal iliac vein thrombosis, presumably occurring in pregnancy, is plausible in this group of patients, we know of no evidence that this is so, and, with modern duplex scanning, one would have expected to see other evidence of previous deep vein thrombosis.

Is it not more likely that the condition, which undoubtedly exists, is analogous to varicocoele and gonadal vein reflux in men?

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- 1 Hobbs JT. Treatment of vulval and pelvic varices. In: Bergan JJ, Yao JST, eds. *Venous Disorders*. Philadelphia, Pennsylvania: W. B. Saunders, 1991; 253–7.

Book reviews

Xeno-Transplantation

D. K. C. Cooper, E. Kemp, J. L. Platt and D. J. G. White (eds). 240 × 165 mm. Pp. 854. Illustrated. 1997. Heidelberg: Springer. £184.50.

This book is really a collection of monographs from most of the well known contributors to the field of xeno-transplantation. The standard of contributions varies from excellent to fairly dismal. There appears to have been no attempt by the editors to co-ordinate the contributions in any way and so the amount of repetition is considerable. Although this can be tedious, it does give each chapter a sense of completeness, which means one can choose a topic to read and get most of the relevant text and references together. It is also interesting to compare the different explanations and ideas about the same immune processes described by different authors. This book is really the only text that covers the field, but xeno-transplantation is advancing more rapidly than most other areas of biological research and the inevitable 1- to 2-year gap to publication means that, already, some of the contributions seem outdated. Nevertheless, to those with a genuine interest in xeno-transplantation, this book is Hobson's choice – an essential purchase.

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Surgery of the Colon and Rectum

R. J. Nicholls and R. R. Dozois (eds). 286 × 224 mm. Pp. 929. Illustrated. 1997. Edinburgh: Churchill Livingstone. £185.

Ever since the final publication of John Goligher's textbook in 1984, there has been an unfilled niche in the market. This new offering, a worthy attempt to fill that niche, is a multiauthor publication with contributions from around the world. The book is well up to date in most areas, covering recent developments like pouchitis, adjuvant treatment of colorectal cancer and newer surgical techniques, such as transanal endoscopic, laparoscopic and sphincter replacement surgery, and the use of a colon pouch. The coverage of areas such as rectal prolapse and solitary rectal ulcer syndrome is excellent as is that of familial adenomatous polyposis. A large section of the book is devoted to assessment of the colon and the rectum, with a clear and comprehensive discussion of the role of anorectal physiology. The coverage of 'traditional' complaints such as haemorrhoids, fissures and fistulas is superb. Controversial areas in the treatment of colonic cancer, such as no-touch technique, extended lymphadenectomy and high ligation are discussed, but I was disappointed to see no real detail given on a method of anastomotic technique. I was also slightly disappointed with the description of the technique of anterior resection, a key operation in colorectal surgery. None the less, this volume has been worth the wait and will find a place on the bookshelf of most coloproctologists and trainees.

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An Introduction to the Symptoms and Signs of Surgical Disease

N. L. Browse. 246 × 189 mm. Pp. 456. Illustrated. 1997. London: Arnold. £24.99.

This popular textbook of surgical symptoms and signs is now presented as a third edition, in a new, modern format. The content has not changed greatly from previous editions, where the emphasis was on the skills required to build up a full surgical history and elicit the necessary abnormal physical signs, enabling the junior surgeon to make a sensible diagnosis and consider sensible methods of treatment. The style is dogmatic, advocating a consistent approach to the history and examination of the various bodily systems. This consistency makes it very easy to read and take in the essential information which is presented with great clarity. The undoubted experience of the author in teaching generations of medical students and junior surgeons is evident, the more confusing concepts, such as examination of hernias of various types, are clearly explained and illustrated. The new format benefits from colour printing and computer graphics, and a new layout with coloured revision panels gives a strong visual impact; it is a user-friendly book. It is difficult to find fault with any aspect of the volume, although some of the histories are lengthy and focus on the salient points is occasionally lost. Clinical skills are learned by seeing patients and practising the art of history taking and clinical examination, but a vital accompaniment to this is a comprehensive text. This book is, arguably, the best there is. I recommend it strongly to all medical students and surgical trainees, who will find it very useful throughout their surgical careers.

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Inflammatory and Thrombotic Problems in Vascular Surgery

R. M. Greenhalgh and J. T. Powell (eds). 250 × 175 mm. Pp. 472. Illustrated. 1997. London: W. B. Saunders. £75.

This book is an eclectic collection of 37 essays, all topical and of most interest to vascular surgeons. It is based on a series of presentations at a symposium in London, although this is not made apparent in the book. The principal emphasis is on various aspects of abdominal aortic aneurysms and venous thrombosis, together with a number of articles on relatively rare conditions like Buerger's or Takayasu's disease, and a series of chapters on common problems like vein graft stenosis. Its title is slightly misleading. While some chapters deal with the recent advances in our understanding of the link between inflammatory response and vascular disease, the majority deal with the clinical problems arising from thrombosis, without any link to the basic sciences. The actual approach to each topic also varies widely. Some chapters are simply a description of work carried out in a particular laboratory, while others are much wider general reviews. The chapters on the basic sciences and vascular disease are extremely well written, and should be comprehensible and interesting to all vascular surgeons who wish to keep up to date with the latest advances in vascular biology. This is not, and does not pretend to be, a general reference book about vascular surgery or all the recent advances in vascular biology connected

with the inflammatory response, but it should make interesting reading for all vascular surgeons.

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Year Book of Thoracic and Cardiovascular Surgery – 1997

R. J. Ginsberg, A. S. Wechsler and W. G. Williams (eds).
235 × 160 mm. Pp. 421. Illustrated. 1997 St Louis,
Missouri: Mosby. £57.

The increasing number of specialty journals and publications each year leaves the busy clinician with the dilemma as to which journals should be read regularly and which should be referred to for an individual problem. The Year Book series endeavours to survey a large number of journals and to offer the reader a selection of papers from them in the form of abstracts; an important commentary from an invited specialist in the field is added. The publishers could not have done better than to invite Doctors Ginsberg, Wechsler and Williams to edit this book. A quick glance suggests that the vast majority of papers come from the *Annals of Thoracic Surgery* and the *Journal of Thoracic and Cardiovascular Surgery*. However, detailed study reveals several articles culled from other specialist journals, implying that cardiothoracic surgeons would do well to have a wide reference base if they are to keep abreast of developments. The book is divided into sections on general thoracic surgery, adult cardiovascular surgery, and cardiac surgery for congenital conditions. Transplanters will be pleased to know that their field is covered adequately under both adult and congenital conditions. There are an additional 58 pages of subject and author indices. The former includes titles for both 1996 and 1997, so that the reader will know if any subject has been dealt with in the 1996 Year Book and be able to delve into the previous volume before rushing off to visit a web site. The volume is well produced in easily readable print size. Where relevant, the editors have included diagrams and illustrations to strengthen the abstracts. Most hospital libraries already stock Year Books on their shelves. Every cardiothoracic surgical department should ensure that this volume is added to their series.

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Clinical Anatomy: A Revision and Applied Anatomy for Clinical Students

H. Ellis. 245 × 172 mm. Pp. 534. Illustrated. 1997. Oxford: Blackwell Science. £29.50.

Professor Ellis continues to fine-tune and upgrade this classic textbook of clinical anatomy. The latest edition utilizes the recent advances in imaging techniques, in particular magnetic resonance imaging. The many illustrations have been improved considerably by more liberal use of colour. Harold Ellis is to be congratulated on continuous refinement and improvement on a topic which, regrettably, is tending to be neglected in undergraduate medical education. In addition to the essential clinical information, I found the glossary of eponyms at the end of the volume both entertaining and educational. This book is a classic

and I would be intrigued to see how Harold Ellis can improve the next edition. No general surgeon should be without a copy, updating your old edition to the ninth is money well spent.

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Finals in Surgery: A Guide to Success in Clinical Surgery

A. N. Thompson and K. G. M. Park. 215 × 139 mm. Pp. 238. Illustrated. 1997 Edinburgh: Churchill Livingstone. £12.50.

This is a pocket-sized textbook (at least it will fit into the medical student's white coat pocket) which is divided into three sections. The first section deals with the general principles of the final examination in surgery and begins with advice on personal presentation, the examiners, and ends with a list of examiners' favourites. The second section deals with approach to cases, from lumps and bumps to chest cases, and outlines the correct approach to those that crop up frequently in finals. There are one or two small errors in this section, on rare conditions, which I am sure the authors will correct or omit in the next edition. The last section, which I think will be the student's favourite, is entitled 'miscellaneous' and covers such topics as trauma and resuscitation, fluid balance, surgical tubes, drains, etc. and finishes with a section on radiology. Some of the radiographs in the radiology section are of poor quality; even when I was aware of the answer, the findings were too subtle and certainly not something I would put up in front of a nervous medical student. I have no doubt that this volume will be very popular with students taking their final surgical examination. As well as imparting some sound advice on how to approach the examination, it covers well the cases that a medical student is likely to come across. This is the book we would all have liked to have in the weeks and days before our final examination in clinical surgery.

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Scientific Foundations of Trauma

G. J. Cooper, H. A. F. Dudley, D. S. Gann, R. A. Little and R. L. Maynard (eds). 276 × 210 mm. Pp. 767. Illustrated. 1997. Oxford: Heinemann. Price not supplied.

A very large number of textbooks on the subject of trauma have come on to the market in the past few years. Most of these relate to the surgical management of various types of trauma, but the mechanisms of injury are seldom explained clearly and the reader has to access quite a large number of other sources to gain an appreciation of mechanism of injury. This book does just that for the reader. It is an extremely comprehensive treatise on

the effects of various blunt and penetrating injuries on the human frame. As such, it could almost be described as a textbook of pathology, but there is plenty of information on the general and local responses to injury and its treatment, as well as on basic anatomy, and physiology. Military injuries are well covered as are civilian problems, and there is considerable information on prevention and protection. I can thoroughly recommend this book as it provides an almost unique insight into the mechanisms of trauma.

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Superficial Bladder Cancer

F. Pagano and W. R. Fair (eds). 289 × 194 mm. Pp. 228. Illustrated. 1997. Oxford: Isis Medical Media. £59.95.

This well produced volume offers a topical, state-of-the-art view of superficial bladder cancer (SBC). Beginning with an excellent chapter on the epidemiology of SBC, it proceeds to a discussion of bladder cancer as a molecular disease. William Murphy's contribution on the pathology of SBC is generally good but many of the points he raises are dealt with elsewhere, a common failing in multiauthor books. Prognostic factors are capably examined by Yves Fradet, who also has the foresight to introduce us to the concept of bioeconomy in bladder management. Intravesical therapy is dealt with thoroughly, including an excellent chapter on biological response modifiers. Finally, there are contributions on the relative roles of intravesical chemotherapy and immunotherapy, and the management of unresponsive SBC, T1 tumours and carcinoma *in situ*. The excellent debate on conservative *versus* aggressive treatment for these conditions reminds us that there still remains a deal of 'art' in surgical management. This view is maintained in the thoughtful contribution by Paul Abel on the follow-up of patients with SBC. In summary, this is a book for the urologist with an interest in SBC. The subject is treated with a commendable

thoroughness, which makes it an ideal source for any clinician involved in dealing with this common disease.

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The Thyroid: Fine-Needle Biopsy and Cytological Diagnosis of Thyroid Lesions

S.R. Orell and J. Phillips (eds). 245 × 174 mm. Pp. 205. Illustrated. 1997. Basel: S. Karger AG. US\$97.50.

It is particularly appropriate that one of the authors of this excellent text is a Swedish professor of pathology working in Australia, as the wide acceptance of fine-needle biopsy (FNB) of the thyroid owes much to the seminal work of Scandinavian pioneers such as Franzen, Zajicek and Lowhagen. This is a well written book that clearly states the aims of FNB and, particularly, its role in the management of thyroid nodular disease to identify with high accuracy the benign lesion, that can be treated conservatively, from the malignant lesion. It is quite rightly stressed that FNB does not replace more formal histology and should be regarded primarily as a supplement to clinical examination. The crucial role of the pathologist and the need for an integrated biopsy clinic if optimum results are to be obtained are well described, along with important technical aspects of FNB. The overlap of subject matter in chapters 6 and 7 dealing with the cell types found in FNB smears and the architectural and cytological findings in specific thyroid diseases, does not detract in any way from the value of this book. The latter chapter is quite superb and is well illustrated; first-class summaries of the diagnostic findings in each condition are followed by practical caveats outlining limitations and pitfalls. Newer techniques, such as proton magnetic resonance, which may add to the utility of FNB particularly in the diagnosis of follicular tumours, are appropriately included. Although the authors state that this text is not intended to be a comprehensive reference book it does, nevertheless, achieve this objective. It will be of enormous value to all who are involved in the management of patients with endocrine disease involving the thyroid gland.

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Notices and announcements

25 February–1 March 1998

IX Asean Congress of Plastic Surgery
Penang, Malaysia

Information: M. Subramaniam,
Department of Plastic Surgery, Hospital
Ipoh, 30990 Ipoh, Perak, Malaysia

26–27 March 1998

3rd M62 Coloproctology Course
Manchester, UK

Information: J. Hill, Department of
General and Colorectal Surgery, Central
Manchester Healthcare Trust, Oxford
Road, Manchester M13 9WL, UK

20–22 April 1998

**The Paediatric Oesophagus. An
Interdisciplinary Symposium. Main
Topic: Gastro-Oesophageal Reflux
with a Special Interest in Alkaline
Reflux**

Izmir, Turkey

Information. O. Mutaf, Department of
Paediatric Surgery, Ege University Faculty
of Medicine, 35100 Izmir, Turkey

13–15 May 1998

**Association of Surgeons of Great
Britain and Ireland**
Edinburgh, UK

Information. Association of Surgeons of
Great Britain and Ireland, The Royal
College of Surgeons of England, 35–43
Lincoln's Inn Fields, London WC2A 3PN,
UK

20–24 June 1998

**Therapeutic Options for the Locally
Advanced Non-Small Cell Lung
Cancer**

Terme di Valdieri, Italy

Information: G. Buccheri, Scientific
Secretary, Ospedale A. Carle, 1-12100
Roccavione (CN), Italy

12–17 July 1998

**XVII World Congress of the
Transplantation Society**
Montréal, Canada

Information: L. Felicissimo and Associates,
12449 rue Cousineau, Montréal, Québec,
Canada H4K 1P9

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Following final approval of articles, you will be asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Please send us digital versions of your figures. Ideally, these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* 1997; 336: 309–15, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript must have a 200-word structured abstract. Lengthy manuscripts are likely to be returned for shortening. The discussion in particular should be clear and concise and should be limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission signed leading articles which are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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On the title page give: (1) the title of the article, (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

Tables and illustrations

Submit three copies of all illustrations and tables. Type each table on a separate page with an appropriate brief title. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Include explanations of symbols and shading in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work give the original source in full. Obtain permission to use published work from the original author and the publisher before submission

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10000 Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782-4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637-9)

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '*t* = 1.34, 16 d f, *P* = 0.20'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ¹ or ¹⁻³. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984, 66: 184-6. The sequence for the chapters of a book should be: author(s), chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123-63

Leading articles

Resectional surgery for gallbladder cancer

Gallbladder cancer, the commonest biliary tract malignancy, carries a very poor prognosis. Although many authors^{1–3} have recently reported long-term survival rates of more than 50 per cent at 5 years after resectional surgery, such reports need careful evaluation. Survival depends on the ability to achieve a curative (R_0) resection; the overall 5-year survival rate in a recent report was 52 per cent after curative resection, compared with only 5 per cent after non-curative resection². In another recent report, the 5-year survival rate after curative resection in 23 patients with advanced cancer was 20 per cent, but none of the 21 patients who had non-curative resection survived for 2 years⁴. Whether to perform resection or not is largely decided on the basis of evaluation of tumour status and nodal involvement.

If resection is to be curative in patients with disease beyond the gallbladder wall (T_3 , T_4), it should include hepatectomy (segments IVb and V) or even extended right hepatectomy. Bile duct may also be resected if it is involved, but bile duct infiltration carries a poorer outlook. In one study curative resection was possible in only seven of 26 patients with bile duct infiltration compared with 14 of 15 in whom the bile duct was not involved; the mortality rate was higher (27 *versus* 13 per cent) and no patient with bile duct infiltration survived for 3 years⁴. The role of resectional surgery for T_3 and T_4 lesions is controversial as most authors report that patients with serosal involvement do not survive for 5 years even when major resections, including hepatectomy, are performed^{3,5,6}. Overall 1- and 3-year survival rates in patients with T_3/T_4 tumours are 24 per cent⁵ and 7 per cent⁶ respectively. Among the 5-year survivors, nine of ten in one report³ and 15 of 17 in another⁷ were those who did not have serosal involvement. The role of adjunctive radiotherapy and chemotherapy following non-curative resection needs evaluation⁸.

At operation, regional lymph nodes should be examined by frozen section; involvement of the coeliac, superior mesenteric and para-aortic nodes precludes an R_0 resection and predicts poor prognosis, as no patient with involvement of these nodes is likely to survive for 5 years⁶. Surgical resection may, therefore, not be indicated in these patients. Although there are a few anecdotal reports of long-term survival after major resection, including pancreaticoduodenectomy in patients with positive pancreaticoduodenal lymph nodes (N_2), resection can be recommended only if nodal involvement is confined to the hepatoduodenal ligament (N_1)⁹. In a recent report, involvement of even N_1 nodes was associated with poor prognosis; no patient survived for 2 years¹.

Incidental gallbladder cancer, detected for the first time on histological examination after cholecystectomy for presumed gallstone disease, is likely to be early (T_1) but it may be locally advanced although still confined to the gallbladder (T_2). There is general agreement about the need for reoperation and resection for T_2 disease, as more than half of the affected patients are likely to have nodal metastasis^{2,5,6}. Resection should include a non-anatomical wedge of the liver in the gallbladder bed, with 2-cm margins, and dissection of lymph nodes in the hepatoduodenal ligament and the posterosuperior pancreaticoduodenal nodes (extended cholecystectomy); some authors also recommend resection of the bile duct to ensure adequate nodal dissection^{2,5}. The 3-year survival rate after extended cholecystectomy in patients with T_2 tumours is 91 per cent, compared with 28 per cent after simple cholecystectomy⁵.

Management of early (T_1) incidental cancer, however, remains controversial. While many authors report long-term survival after simple cholecystectomy and do not recommend reoperation for such disease^{1,6}, some have observed locoregional recurrence after simple cholecystectomy for early cancer⁷. This is because some patients with presumed early disease (especially those with involvement of the muscle, T_{1b}) may have lymph node involvement and may actually have locally advanced disease. The first lymph nodes to be involved in gallbladder cancer are either cystic or pericholedochal; while the cystic lymph node may be included in

the specimen, pericholedochal nodes are not available for histological examination after simple cholecystectomy. Some patients with incidental cancer may, therefore, be understaged and undertreated. It may be better to reoperate and perform extended cholecystectomy even in patients with such early incidental cancer^{2,10} as this offers the only chance of cure.

Most cholecystectomies for gallstone disease are now being carried out laparoscopically and if the gallbladder harbours a cancer there is a high risk of port-site or peritoneal recurrence. Open cholecystectomy should, therefore, be advised if there is any suspicion of gallbladder cancer before surgery (irregular thickening of the gallbladder wall, large sessile polyp). If cancer is suspected during laparoscopic dissection (dense adhesions, difficult dissection) the procedure should be converted to an open operation. If histological examination after laparoscopic cholecystectomy reveals cancer, reoperation and resection should be performed as outlined above; the port of extraction of the gallbladder should also be excised or irradiated.

Recent reports of long-term survival after resectional surgery in patients with gallbladder cancer are encouraging, but critical appraisal shows that these results are obtained in a small minority of patients who have disease confined to the gallbladder and to the lymph nodes in the hepatoduodenal ligament. Once the disease has spread beyond the gallbladder or to the distant lymph nodes, as is usually the case, the outlook remains poor. The role of resectional surgery in these patients requires further prospective evaluation.

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- 1 Bartlett DL, Fong Y, Fortner FG, Brennan MF, Blumgart LH. Long term results after resection for gall bladder cancer. *Ann Surg* 1996; 224: 639–46.
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- 10 Onoyama H, Yamamoto M, Tseng A, Ajiki T, Saitoh Y. Extended cholecystectomy for carcinoma of the gall bladder. *World J Surg* 1995; 19: 758–63.

Genetic predisposition to breast cancer

In Western society there are many women who think that they may be at increased risk of developing breast cancer because of a family history; they ask for advice. There often follows referral to a breast clinic where those at increased risk can be identified. Many of the fears that these women have are groundless but it is important that a specialized breast service can identify those at risk and counsel them accordingly. As this is a rapidly developing field, with an increasing understanding of genetic aspects, it may be difficult to provide the advice that is needed. It is therefore important that breast specialists develop a common strategy and collect information about incidence and outcome.

Any management strategy must be provisional because there is so much that is unknown, but without an identified way of defining high or moderate risk, and without a uniform management plan, there will be no progress. Women should be warned that there are no clear answers. This presents psychological dilemmas as patients prefer clear information presented with confidence and security. Whatever management strategy is proposed may be incorrect; this creates an ethical dilemma, but so does doing nothing. It is therefore vital to record strategy, treatment and outcomes.

What are the risks?

Information from the Cancer and Steroid Hormone Case–Control Study¹ and the Breast Cancer Detection Demonstration Project² allows an estimate of risk to be made. For example, a woman aged 50 years who has a sister with breast cancer has an estimated lifetime risk of 3.6 (95 per cent confidence interval (c.i.) 2.1–6.1), but a woman aged 50 years with both a mother affected premenopausally and a sister affected has an estimated lifetime risk of 17.1 (95 per cent c.i. 9.4–31.3). Gail *et al.*³ have constructed a projected probabilities table which may be used to estimate individual risk. The risks can be categorized as follows: (a) high risk – women in families with four or more relatives affected with either breast or ovarian cancer in three generations and one living affected individual; and (b) moderate risk – three first- or second-degree relatives with breast or ovarian cancer on the same side of the family, or two first- or second-degree relatives with breast cancer diagnosed under the age of 60 years, or one first-degree female relative with breast cancer diagnosed under the age of 40 years, or one or more first-degree relatives with bilateral breast cancer.

What can be offered to women at risk?

It might be argued that there is very little that can meaningfully be offered. If a woman has a high risk, bilateral mastectomy might be considered, with or without reconstruction. This does not guarantee the removal of all breast epithelium and, although the risk might be lowered⁴, it is not abolished. Women at high or moderate risk might be offered tamoxifen chemoprevention, but the benefit of this is unproven. When the International Breast Intervention Study and similar trials are completed, more information will be available but results and conclusions will not be ready for 5 years. Annual clinical examination and mammography can be offered but evidence suggests that such screening is not effective in younger women; nevertheless it might be effective in a group at high or moderate risk. The predictive value of genetic testing for mutations of the *BRCA1* and *BRCA2* genes is not clear. Women with breast cancer with such mutations have a 65 per cent risk of contralateral malignant breast disease⁵, but the chance that a woman from a breast cancer family carries a mutation⁶ is only seven in 100. It is unlikely that genetic testing, in the present state of knowledge, would alter management.

Management strategy

Despite these problems, breast surgeons should develop a common management strategy and collect data that emerges from it. Such a strategy should be capable of

adjustment as and when new information becomes available. A possible plan might be as follows:

- 1 All women at high risk
 - Annual mammography
 - Teaching of breast self-awareness
 - Tamoxifen chemoprevention trial
 - Consultation with medical geneticist and discussion of bilateral mastectomy
 - (Gene testing not indicated⁷)
- 2 Women aged 30–35 years at moderate risk
 - Annual mammography from 5 years below the age of the youngest relative with breast cancer (if the patient is over 30 years old)
 - Teaching of breast self-awareness
- 3 Women aged 35–50 years at moderate risk
 - Annual mammography
 - Teaching of breast self-awareness
 - Tamoxifen chemoprevention trial
- 4 Women aged over 50 years at moderate risk
 - Mammography every 3 years in the National Health Service breast screening programme
 - Teaching of breast self-awareness
 - Tamoxifen chemoprevention trial

Such a programme may be hypothetical and empirical but no apology is tendered. National organization and planning is needed to replace the current variability and uncertainty, and to measure the effectiveness of this strategy.

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Review

Colorectal cancer vaccines

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Background Advances in molecular pathology have enabled a number of colorectal cancer antigens to be identified and characterized. The commonest investigated include 17-1A, 791Tgp72 and carcinoembryonic antigen. Vaccines have been developed that stimulate the immune system to target these antigens. This paper reviews current areas of research in this field.

Methods and Results Relevant articles were obtained on vaccines for colorectal cancer from Medline and the Bath Information Data System. A number of approaches are currently being evaluated in Phase I, II and III trials. These include anti-idiotypic antibody immunization, DNA vaccines, mucin and heat shock protein-based vaccines, oncogenes and viral vectors.

Conclusion Evidence is accumulating to suggest that immune responses may be generated against colorectal cancer using these approaches. While the concept of vaccination against this malignancy is essentially experimental, surgeons should be aware of current advances.

Colorectal cancer is the second commonest cause of cancer death in the UK, accounting for approximately 16000 deaths per year¹. Despite advances in surgery, chemotherapy and radiotherapy, only modest improvements in overall mortality rate have been achieved in the past 30 years. Cancer vaccines offer a potentially new treatment option. Encouraging results were originally noted in a number of cancers using autologous tumour and the cytokine interleukin (IL) 2². This approach was, however, hampered by toxicity and the limitations of processing the patient's own tumour. Specific antigens on tumour cells have now been identified and a variety of approaches have been developed to induce immune responses against them. The aim of this review is to evaluate critically current strategies aiming at active vaccination against colorectal cancer.

Tumour-associated and tumour-specific antigens

Immune responses may be induced either by B cells or T cells. The former is a humoral response that leads to antibody production, while the latter is termed cell-mediated immunity. Animal studies have shown that tumour regression is more commonly associated with the induction of cellular rather than humoral immunity³. For T cells to recognize antigen, the antigen must be taken up and digested by specific antigen presenting cells (APCs). It is then bound to glycoproteins, encoded by the major histocompatibility complex (MHC), and presented on the surface of the APC in conjunction with co-stimulatory molecules. Tumour cells are poor immunogens, as they lack co-stimulatory molecules, and have low expression of the necessary MHC molecules. Vaccines aim to target APCs more effectively than tumour cells, thereby stimulating a T cell response.

There are two main types of T cell. Cytotoxic T lymphocytes (CTLs) express the surface marker CD8 and recognize peptides presented by APCs bound to class I MHC glycoproteins. Once stimulated they will proliferate, migrate to the tumour site and kill any cell that expresses

the same peptide. The second type, CD4-positive helper T cells, provide the cytokines necessary to activate and allow CTL proliferation. Recognition of antigen in their case is in association with class II MHC glycoproteins (*Fig. 1*). An effective tumour vaccine should stimulate both cytotoxic and helper responses.

Two categories of antigen, or epitope, are present on the surface of colorectal cancer cells: tumour-associated antigen (TAA) and tumour-specific antigen (TSA). The former may occur as a result of overexpression of a normally expressed antigen, re-expression of antigens normally repressed in differentiated tissue, or an antigen may be expressed on tissue where it is not normally present. They are not confined to a single type of malignancy; 791Tgp72 is, for example, a TAA that occurs on osteosarcomas as well as colorectal and ovarian tumours. TSAs such as K-RAS form either through cellular mutations or by the expression of viral glycoprotein envelopes on cell membranes⁴.

This review concentrates on the most widely investigated antigens present on the surface of colorectal cancer cells, 17-1A, 791Tgp72 and carcinoembryonic antigen (CEA), and the ways in which immune responses have been generated against them. Vaccination involves anti-

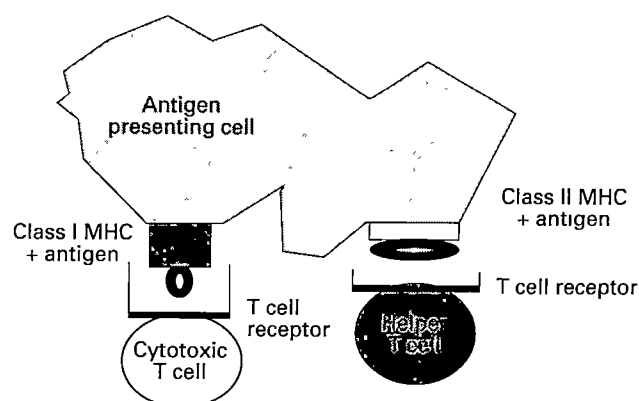


Fig. 1 Antigen presentation to cytotoxic T cells and helper T cells. MHC, major histocompatibility complex

idiotypic antibodies that mimic tumour antigen, and polynucleotide-mediated immunization where DNA or RNA encoding epitope is inserted into the cell genome. Vaccines may also be based on peptides encoded by oncogenes. In addition, this review considers mucin and heat shock proteins (HSPs) as vaccines.

17-1A antigen

The 17-1A antigen was first isolated from a colon carcinoma cell line by immunoprecipitation with the 17-1A monoclonal antibody⁵. It is a 37–40-kDa cell surface glycoprotein present on over 90 per cent of colorectal cancers. It exists in various configurations, depending on the level of glycosylation, and is thought to be involved in cellular adhesion. Passive serotherapy using monoclonal antibodies against this antigen prolongs survival in patients with primary tumours⁶. These results are currently being tested in a multicentre phase III study in patients with stage III (Dukes C) tumours. There are, however, a number of ways in which active immunity and T cell responses can be elicited against CO17-1A.

Immunization with anti-idiotypic monoclonal antibodies may offer an alternative immunological approach to tumour therapy. The theoretical basis of this treatment modality is outlined in the network hypothesis of Lindenmann and Jerne⁷. The premise is that antibodies (Ab1) against TAAs have specific idiotypes in their variable regions. The anti-idiotypic monoclonal antibody (Ab2) is an antibody against this idiotypic and must therefore 'mimic' the antigen on the surface of the tumour cell (Fig. 2). The concept of the anti-idiotypic antibody acting as an 'internal image' of the antigen suggests that this novel presentation of tumour epitope should elicit an immune response^{8–10}. This approach has a number of advantages over other forms of immunotherapy. Anti-idiotypic monoclonal antibodies may be presented by APCs in the context of class I and II MHCs, thus eliciting both cytotoxic and helper T cell responses. Presentation of the epitope in a different molecular environment may also act to break any tolerance that may have developed to the weakly immunogenic TAAs¹¹. Anti-idiotypic monoclonal antibodies have a longer half-life in the peripheral blood and are resistant to proteolytic digestion. They can also be used when the TAA is either

unknown, or difficult to purify in the quantity required. In addition, there is *in vitro* evidence that the anti-idiotypic antibody may be more effective in eliciting an immune response than the actual antigen^{12,13}. The former is also free from the potential dangers of retroviruses and genetic manipulations.

A polyclonal anti-idiotypic antibody to CO17-1A has been developed, and 30 patients with advanced colorectal cancer have been immunized^{14–16}. Humoral responses were noted, and all had evidence of Ab3 production. This antibody showed identical binding of tumour cells as that observed with Ab1. Six patients had partial clinical remission and a further seven had arrest of metastases following treatment. Of these 13 patients, nine also received chemotherapy, making conclusions about the efficacy of Ab2 contentious. A follow-up trial used a different goat polyclonal antibody in 12 patients who had undergone resection of the primary tumour¹⁷. Six of these patients developed antibodies against the anti-idiotypic antibody and two had antigen-specific T cells, which proliferated in culture on stimulation with the CO17-1A antigen. In addition, seven of the original 12 had tumour remission lasting from 1.1 to 4.1 years after immunization. Cellular immunity has been noted in a further patient with advanced colorectal cancer¹⁸ following immunization with SCV106, a goat anti-idiotypic monoclonal antibody that also mimics the TAA 17-1A. This patient had two lung metastases from a previously resected colonic carcinoma which were removed after completion of the antibody course. Antibodies eluted from the resection specimen were confirmed to be against the tumour antigen in a conventional enzyme-linked immunosorbent assay, and immunohistochemical analysis of tissue showed massive infiltration of T helper and cytotoxic T cells.

Recent work has shown how passive immunotherapy with unconjugated monoclonal antibodies may give rise to an idiotypic network response that correlates with clinical outcome¹⁹. Twenty-four patients with metastatic colorectal cancer were treated with monoclonal antibody 17-1A (Ab1). After completion of therapy, five of the patients had peripheral blood T cells specifically recognizing human antimonomoclonal antibody 17-1A idiotypic antibodies. These same five patients were the only ones in the study who had any objective tumour regression following monoclonal antibody therapy. The association between the presence of anti-idiotypic reactive T cells and clinical response was statistically significant.

Clinical responses have clearly been demonstrated using anti-idiotypic antibodies. The major disadvantage of this approach is that the tumour itself must express the antigen that the antibody is mimicking. If it does not, a vaccine based on this approach will not work.

Tumour-associated antigen 791Tgp72

The anti-idiotypic monoclonal antibody 105AD7 mimics the TAA 791Tgp72, present on 80 per cent of colorectal cancers²⁰. Thirteen patients with liver metastases from colorectal cancer were recruited to a phase I study. No treatment-related toxicity was observed and patients receiving the vaccine lived for a median of 12 months, significantly longer than a contemporary group of patients²¹. In addition, nine of the 13 showed either a T cell blastogenesis response against cell lines expressing 791Tgp72 or evidence of IL-2 production. Those patients who had the best immune response lived the longest. A

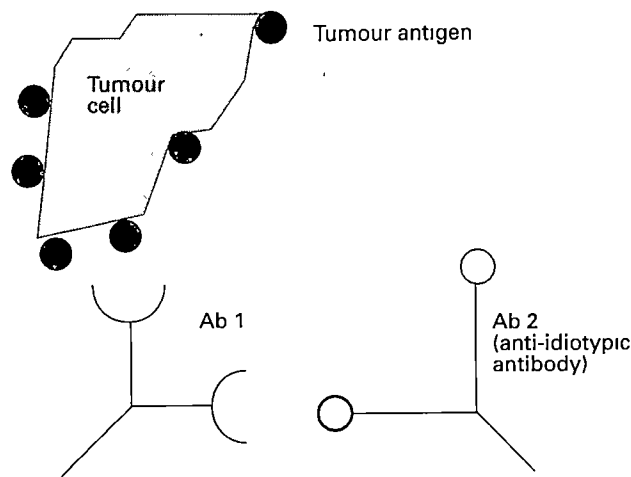


Fig. 2 Anti-idiotypic antibody immunization. Ab, antibody

randomized, double-blind survival study in patients with advanced colorectal cancer has recently closed, recruiting 162 patients to either 105AD7 or placebo arms; results are awaited. 105AD7 has also been used in an adjuvant setting and given to patients with primary colorectal cancer before surgery. Enhanced killing of autologous tumour by natural killer (NK) cells and non-NK effectors has been observed²². Increased tumour infiltration by lymphocytes expressing CD4, CD8, CD56 and CD25 has also been noted^{23,24}.

Evidence is accumulating that anti-idiotypic antibody therapy induces an immune response against antigens present on tumour cells. The low toxicity and the lack of requirement for processing of autologous tumour are advantageous. However, tumour cells not expressing the antigen that the anti-idiotypic antibody mimics may escape killing, thereby reducing the efficacy of the vaccine.

Carcinoembryonic antigen

CEA is one of the best characterized tumour marker antigens in terms of its tissue distribution, biochemistry and molecular structure^{25,26}. It is expressed extensively in humans on the majority of colorectal, gastric and pancreatic carcinomas, as well as on approximately 50 per cent of breast cancers and 70 per cent of non-small-cell lung cancers. CEA is also expressed to some extent on normal colon epithelium and in some fetal tissues²⁷. At the amino acid level CEA shares approximately 70 per cent homology with non-specific cross-reacting antigen (NCA) which is found on normal granulocytes^{28,29}. However, CEA is highly overexpressed on tumour cells and is therefore a potential target for active immunotherapy. The immunogenicity of CEA in humans is at best controversial. Several studies claim to have detected antibodies to CEA in patients, while others have questioned the validity of such assays³⁰. The first evidence that T cells from patients with cancer could recognize and respond to CEA was demonstrated *in vitro* by immunization with an anti-idiotypic antibody which mimics CEA³¹.

A phase I clinical trial in patients with advanced colorectal cancer, using the anti-idiotypic antibody 3H1, demonstrated anti-CEA antibody responses in nine of 12 patients, with four showing T cell proliferation against CEA³⁰. Toxicity was limited to local reaction with mild fever and chills. Studies are now focusing on treating patients with minimal residual disease.

Instead of using anti-idiotypic antibodies as surrogate antigens, the CEA gene has been cloned in baculovirus and recombinant protein has been used as the immunogen. This may be advantageous as the patient's APCs can process, present and select the most appropriate T cell epitopes. It has, however, the disadvantage that immune responses may be generated to the region of CEA which is homologous with NCA, causing granulocyte toxicity. Two clinical studies have been carried out using recombinant CEA. Two of five patients with breast cancer showed CEA-specific proliferative responses, with one having a CEA-specific delayed type hypersensitivity (DTH) response³². In a follow-up study, the addition of the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) to CEA enhanced the proliferative responses to CEA from two of six patients to six of six³³. No toxicity was observed.

A new approach to vaccination, which has been very successful in infectious diseases, is polynucleotide immunization. DNA or RNA can be administered by intramuscular injection, allowing myocytes to take up the DNA and express the gene product. The released protein is taken up by APCs which migrate to the draining lymph nodes and present antigen to the T cells³⁴. An alternative route of immunization is intradermal injection; it is presumed that the DNA is taken up by Langerhans cells, which then act to present the antigen. This leads to a continuous intracellular production of protein antigens that may be presented in association with class I MHC molecules, thereby eliciting CTL responses^{35,36}.

The advantages of DNA vaccines are numerous. They can be easily purified, coated on gold particles and introduced directly into tissues by gene gun (bolistics). DNA may also be combined with genes for cytokines, such as IL-2, IL-6 or IL-7, or GM-CSF, in order to enhance the immune response generated³⁷.

Mice may be immunized with a plasmid encoding the full length complementary DNA (cDNA) for CEA²⁸. Evidence of humoral and cellular responses against the glycoprotein was found in all of five mice immunized and three generated CEA-specific memory T cells. In addition, a further two had IL-2/IL-4 release in response to CEA. Clear evidence exists to support this approach as a potential vaccine strategy and approval has been granted for a phase I trial in colorectal cancer. In the light of recent negative publicity, it remains to be seen how patients will react to the concept of gene therapy for their cancer.

Recombinant vaccinia viruses are being considered for use in the treatment of cancer because it has been shown, in animal models, that co-presentation of a weak immunogen with the highly immunogenic vaccinia proteins can elicit a strong immune response against the inserted gene products³⁸. Animals developed good antibody and cell-mediated immune responses to CEA when they were immunized with complete cDNA of CEA inserted into the vaccinia genome (rV-CEA). A phase I study utilizing this approach in patients with metastatic carcinoma showed for the first time that it was possible to induce cytolytic T cell responses to CEA which killed tumour cells²⁹. However, the immune response to the vaccinia inhibited replication of the recombinant virus at subsequent immunizations, making it impossible to boost the primary immune response to CEA. Animal studies have suggested that this problem may be solved by priming with rV-CEA and then boosting with either recombinant CEA or specific CEA peptides. Clinical trials are planned.

Oncogenes

Peptide vaccines can bind to MHC molecules and elicit immune responses. Generation of CTLs would be further enhanced if the peptide was presented by an APC, such as a dendritic cell³⁹. A murine model has shown that antigen-specific CTLs may be generated following subcutaneous administration of irradiated bone marrow-derived dendritic cells, pulsed with OVA peptide *in vitro*⁴⁰. These results have been confirmed in a separate study, in which β -galactosidase acted as the TAA⁴¹. Immunization of mice with mutant p53 peptide-pulsed dendritic cells, generated from stem cells of other tumour-bearing mice, can induce effective antitumour CTL responses and lead to significant antitumour effects⁴². If the T cell epitope is as yet

undefined, as is the case for a number of cancers, CTLs may still be generated using unfractionated acid-eluted tumour peptides in conjunction with the method outlined above⁴³.

Mutations in codon 12 of *K-ras* are frequently found in pancreatic adenocarcinomas⁴⁴. Mutant p21 ras is, therefore, a TSA that can be recognized by human T cells⁴⁵. Synthetic *ras* peptides have been used in conjunction with APCs as a vaccine for pancreatic cancer, with encouraging results. This approach could also be applied to colorectal carcinomas, which also show mutations in codon 12 of *K-ras*. As an alternative to peptide vaccination, it is possible to clone the peptide epitope as a minigene and use this DNA as the immunogen. Minigenes coding for a single epitope derived from mutant p53 have been demonstrated to elicit CTLs in a mouse model⁴⁶.

Mucins

Human epithelial mucins are a family of high molecular weight glycoproteins that lubricate and protect the underlying gastrointestinal mucosa. They are characterized by a large number of *O*-glycosylated tandem repeat domains which vary in length, number and extent of *O*-glycosylation^{47,48}. Novel mucin epitopes are expressed by tumour cells owing to aberrant glycosylation of pre-existing mucins^{49,50}. This results in shorter sugar side-chains, with concomitant exposure of peptide antigens in the intestinal crypts. Evidence has accumulated to show that T cells specific for native epitopes on the mucin polypeptide core tandem repeat can be expanded *in vitro*^{51,52}. Further work has also shown that a humoral response may be generated, with B cells recognizing the mucin tandem repeats⁵³. Antibodies have, therefore, been detected in the blood of patients with colonic carcinomas, breast and pancreatic tumours⁵⁴.

A vaccine has been formed by transfecting the gene for the TAA (MUC-1) into Epstein Barr virus-immortalized B cells⁵⁵. The latter act as APCs priming cytotoxic T cell precursors and DTH responses occurred in the two chimpanzees immunized. A phase I study using a 105-amino-acid MUC-1 peptide admixed with *Bacillus Calmette-Guérin* has been used recently in 30 patients with advanced colorectal cancer⁵⁶. A number experienced ulceration at the injection site, and systemic symptoms such as fever, rigors and malaise. Immunologically, DTH responses were noted against mucin-specific peptides, and seven of 22 patients tested showed a twofold to fourfold increase in CTLs. Clinically, only two patients had stable disease. Eleven patients with advanced colorectal cancer have been immunized with Theratope sialyl-Tn-KLH (keyhole limpet haemocyanin) cancer vaccine in Detox adjuvant, following low-dose cyclophosphamide therapy⁵⁷. This phase II study demonstrated that patients with higher anti-sialyl-Tn immunoglobulin G antibody titres following vaccination survived longer than patients with lower titres, suggesting an immune response. Data are accumulating suggesting a potential role for mucins as cancer vaccines, although toxicity and the problems associated with processing autologous tumour may preclude their use.

Heat shock proteins

HSPs are a group of proteins present in all living cells. HSP preparations contain a broad array of peptides

tightly bound to HSP molecules^{58,59}. They offer a number of advantages as cancer vaccines. If a lasting therapeutic effect is to be conferred by a vaccine, a CTL response must be generated⁶⁰⁻⁶². Vaccination with HSP-peptide complexes circumvents the need for identification of the antigenic epitopes of cancer cells, as HSPs are naturally complexed with the entire repertoire generated in the cell. Another advantage of such an approach is that an immune response will be generated against all antigens present in the tumour. Furthermore, HSPs require no adjuvants to elicit a CTL response and the complexes can be purified rapidly. As the vaccine is autologous, no material is inoculated to which the patient has not already been exposed thereby reducing the chance of toxicity.

A number of studies have shown that injection of apparently homogeneous HSP preparations from a given tumour into syngeneic rats or mice renders the animals resistant to that particular tumour⁶³⁻⁶⁵. For this treatment modality to be successful, each vaccine would need to be 'custom built' for individual patients, using autologous tumour. Although toxicity would be minimal with this approach, it may nevertheless prove technically difficult, excessively time consuming or expensive. If so, it will not be viable as a vaccine for colorectal cancer. Despite these limitations, phase I studies are currently ongoing.

Conclusion

This review has highlighted how immune responses may be generated against the three most commonly investigated colorectal cancer antigens. It has also considered vaccines based on oncogenes, mucins and HSPs. A number of experimental approaches are apparent, some of which are currently being evaluated in phase I/II studies. It is probable that a number of strategies will fail to become established as treatment options. Surgeons, however, should be aware of these areas of current research and have some understanding of this rapidly evolving field.

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Review

Epidemiology and potential for prevention of abdominal aortic aneurysm

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Background Ruptured abdominal aortic aneurysm (AAA) is a common cause of death which is preventable by elective repair of an asymptomatic AAA.

Methods The literature was reviewed with emphasis on epidemiological studies and population-based screening surveys.

Results and Conclusion The prevalence of small AAA ranges between 3 and 8 per cent. The incidence of asymptomatic AAA seems to be increasing, although exact incidence estimates vary. The most important risk factors for AAA are male sex, age, family history and smoking. Hypertension is associated with a mildly increased risk, but diabetes is not associated with any increase. Primary prevention of AAA is not a realistic option. There is no evidence of an effective medical treatment to prevent growth of small AAAs, although trials with propranolol are under way. The only intervention to prevent death from aneurysm is elective repair of the asymptomatic lesion. Screening for asymptomatic AAA can reduce the incidence of rupture. However, further studies are needed to determine the cost effectiveness of screening compared with that of other health programmes.

Abdominal aortic aneurysm (AAA) ranks as the 13th leading cause of death in the USA and is responsible for 0.8 per cent of all deaths¹. Ruptured AAA accounts for 1.36 per cent of deaths in men and 0.45 per cent of deaths in women over the age of 65 years in England and Wales². These figures are similar to data from the Netherlands³. In men, a peak in the proportional mortality rate owing to ruptured AAA occurs between 65 and 85 years of age; in women, the proportional mortality rate of ruptured AAA continues to rise with age. Most deaths due to rupture are potentially preventable, since elective repair of the asymptomatic lesion can be achieved with a mortality rate of less than 5 per cent^{4–6}. This is in sharp contrast to the reported in-hospital mortality rate of ruptured AAA which varies between 47 and 83 per cent^{6–8}. However, since at least half the patients with rupture do not reach hospital alive, the overall mortality rate of rupture lies between 78 and 94 per cent^{5,9–13}.

The massive difference in mortality rate associated with ruptured and elective aneurysm repair, combined with the easy detectability of asymptomatic lesions, has led to calls for a national screening programme¹⁴. Several screening projects throughout England have shown that such screening is feasible^{15–19}. However, uncertainties about natural history rupture rate, expected increase in life expectancy following surgery and the quality of added life years have so far precluded any firm conclusions about the merits of national screening.

Prevalence

Estimates of the prevalence of AAA can be obtained from population screening surveys and autopsy studies. The prevalence of screen-detected aneurysm in men in England varies between 1.3 and 12.7 per cent^{15,18,20–22}

depending on the age group screened and the criteria used for the definition of AAA (Table 1). A generally accepted pragmatic definition of a small AAA is an aorta with a diameter of 30 mm or more^{17–20,24}, although some have used a stricter definition²⁵. Many differences in prevalence may be explained by differences in definition of an aneurysm²⁶. The prevalence of small AAA ranges from 2.9 to 7.6 per cent if the criterion of an aorta wider than 29 mm is used. This is very similar to the prevalence of screen-detected AAA in other countries in the Western world when the varying criteria are taken into account (Table 2). European and North American experiences differ from that of a Japanese study³². In a screening survey of 348 residents, aged between 60 and 79 years, of a village in central Japan no AAA was detected.

Table 1 Prevalence of abdominal aortic aneurysm in screening surveys in the UK

Location	Sex	Age (years)	No. of patients screened	Criteria for aneurysm (mm)	Prevalence (%)
Oxford ¹⁵	M	65–74	426	*	5.4
Oxford* ¹⁵	M	65–74	426	> 40†	2.3
Liverpool ²¹	M	≥ 55		> 30	2.9
Gloucestershire ²⁰	M	65	4232	> 25	8.4
Gloucestershire ²⁰	M	65	4232	> 40	1.3
Birmingham ¹⁸	M	65–75	2669	> 29	8.4
Birmingham ¹⁸	M	65–75	2669	> 40	3.0
Chichester ²²	M	65–80	2342	> 29	7.6
Chichester ²²	F	65–80	3052	> 29	1.3
Northumberland ²³	M	65–79	628	> 29	6.7
Huntingdon	M	≥ 50	7493	> 29	5.2

In the Oxford study, the criteria for an abdominal aortic aneurysm were a diameter of the infrarenal aorta of more than 40 mm or 5 mm greater than the diameter of the suprarenal aorta

Table 2 Prevalence of abdominal aortic aneurysm outwith the UK

Location	Sex	Age (years)	No. of patients screened	Criteria for aneurysm (mm)	Prevalence (%)
The Netherlands ²⁷	M	>55	2217	*	4.1
The Netherlands ²⁷	F	>55	3066	*	0.7
Norway ²⁸	M	>60	500	†	8.2
Sweden ²⁹	M	74	375	>35	10.7
USA ³⁰	M	60–75	201	>35	9.0
Italy ³¹	M	60–75	741	>29	8.8
Italy ³¹	F	60–75	860	>29	0.6

*The criteria for an abdominal aortic aneurysm in the Dutch study were a diameter of the infrarenal aorta of more than 35 mm or 50 per cent greater than the diameter of the suprarenal aorta
 †The criteria for an abdominal aortic aneurysm in the Norwegian study were a diameter of the infrarenal aorta of more than 29 mm or 50 per cent more than the diameter of the suprarenal aorta

Table 3 Prevalence of abdominal aortic aneurysm in autopsy studies

Location	Age (years)	No. examined	Period	Prevalence in men (%)	Prevalence in women (%)
UK ³³	≥50	1544	1963–1964	2.3	1.6
USA ³⁴	≥50	5244	1950–1984	2.6	1.2
Sweden ³⁵	≥50	45838	1958–1986	4.3	2.1

No measurement criteria on which the diagnosis of aneurysm was based were given in the studies

Prevalence estimates using autopsy methods (Table 3) are remarkably similar to estimates from population screening surveys when similar age and sex groups are compared³⁶. It may be that the unspecified size criteria for a diagnosis of AAA at autopsy are stricter than criteria used in screening surveys. When prevalence rates from autopsy studies are compared with estimates obtained at screening surveys using a stricter definition of an aneurysm, i.e. an aortic diameter greater than 40 mm, it becomes clear that both rates are similar.

Incidence

The reported incidences of asymptomatic AAA in the literature vary between 3.0 and 117.2 per 100 000 person-years^{36–41} (Table 4). All studies report sharp rises in the age-adjusted incidence of AAA in recent years. The average increase in incidence ranges from 4.2 per cent per year in Australia to 11 per cent per year in a report from Rochester, Minnesota, USA. A nationwide study from Denmark reported an increase in the incidence of

Table 4 Incidence of abdominal aortic aneurysm

Location	Period	Data source	Incidence per 100 000 per year		
			Men	Women	Total
Rochester, Minnesota, USA ³⁷	1971–1980	1, 2, 3	—	—	36.5
Western Australia ³⁸	1971–1982	1, 3	117.2	33.9	—
England and Wales ³⁹	1971–1984	1	11.3	3.0	—
Scotland ⁴⁰	1971–1984	1	—	—	63.6
The Netherlands ³⁶	1972–1992	1	37.6	5.5	—

The highest incidence in the reported study period is shown. Data sources: 1, hospital records; 2, death certificates; 3, autopsy reports

Table 5 Trends in the incidence of ruptured abdominal aortic aneurysm

Location	Period	Incidence at beginning (per 100 000 per year)	Incidence at end (per 100 000 per year)	Overall mortality rate (%)
Western Australia ³⁸	1971–1981	3	—	—
Swansea ⁴⁴	1974–1983	7	17	80
Stockholm ⁹	1980	6	—	94
Worthing (UK) ¹⁰	1979–1986	9	18	89
East London ¹¹	1981–1986	13	21	81
Swindon ⁵	1982–1987	9	17	86
Goteborg ¹²	1952–1988	1	7	85

Overall mortality rate was calculated using the sum of the hospital and community deaths from ruptured abdominal aortic aneurysm

asymptomatic lesions from 7.1 per 100 000 to 25.8 per 100 000 person-years from 1977 to 1990⁴². This increase was constant over all age groups examined. Incidence rates were estimated by the number of hospital admissions for elective asymptomatic aneurysm repair. A study from the USA⁴³ reported no increase in the number of hospital admissions for AAA repair after 1985. It concluded that increased case finding, resulting from increased use of ultrasonography, may be one of the reasons for the rise in hospital admissions for AAA repair before 1985. Accurate incidence data for asymptomatic lesions in the community are sparse and unreliable, because valid incidence estimates can only be obtained by screening a defined population for a second time. To the authors' knowledge there is no report in the literature of an incidence estimate based on a second screening round in a large population-based screening programme.

The recent reported incidence of ruptured AAA varies from 1 to 21 per 100 000 person-years^{5,10–12,38,44} (Table 5). The Göteborg study¹² found a sevenfold rise in incidence over a period of 36 years. The age-standardized mortality rate of ruptured AAA also rose by 2.4 per cent per year, indicating that the rise in incidence was not caused by changes in age distribution of the population. Estimated incidence of ruptured AAA through mortality data is less susceptible to changes in diagnostic techniques. However, an increased level of case ascertainment, due to an increased awareness of the condition, cannot be ruled out entirely.

Risk factors

Documented risk factors for AAA are age^{28,34,35,45,46}, male sex^{2,22,34,35,45}, family history^{47–53}, previous vascular

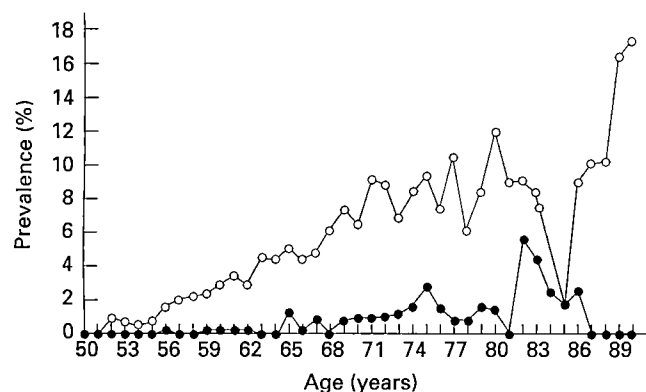


Fig. 1 Prevalence of abdominal aortic aneurysm (AAA) by age on first screening in 10 328 men aged over 50 years. ○, AAA more than 29 mm diameter; ●, AAA more than 49 mm diameter

disease^{54–56}, hypertension^{17,28,46,57–61}, smoking^{58,59,62–66} and hypercholesterolaemia^{28,59,67,68}.

Advancing age is an important risk factor for the development of an AAA (Fig. 1). The mortality rate of ruptured AAA increases with age^{2,43,69}. Several screening surveys have shown that the prevalence of AAA increases with age^{19,22,28,34,35,45,46}. In population screening surveys, an AAA is six times commoner in men than women^{22,27}, but it is only twice as common in men in necropsy studies^{34,35}. In England and Wales, the age-standardized mortality rate of AAA is twice as high in men than women². There is, however, evidence that these sex differences are decreasing³⁶.

Familial clustering of AAA is well described^{49,51,52}. One study reported a greater than tenfold increased risk of developing the condition in men with a first degree relative with an AAA⁷⁰. Others have found a lower relative risk⁷¹. The magnitude of the increased risk in first degree relatives suggests a genetic component, although the influence of a common lifestyle cannot be excluded. A recent molecular genetic study in an Irish population found no significant gene–disease associations⁷².

The best appraisal of the strength of several risk factors for aortic aneurysm comes from population-based screening surveys. In this way, selection bias is minimized and valid comparisons are possible with individuals from the same population with a normal aorta. A Medline search was performed to find all such population-based screening surveys. The numbers of patients with a particular risk factor in the AAA group and the individuals with a normal aorta were extracted from the published reports. The pooled relative risks estimates were calculated using the standard methodology of systematic reviews of randomized clinical trials^{73,74}. We consider a pooled relative risk estimate a useful method of summarizing the available data, although we do not pretend this is a complete meta-analysis of all screening surveys. A summary of the pooled relative risk estimates of several factors associated with AAA is shown in Table 6.

The risk factors most strongly associated with AAA in these population-based screening surveys are male sex and smoking. Patients with peripheral vascular disease and cardiovascular disease are twice as likely to have an AAA than those without these diseases. A positive association with cerebrovascular disease was not found in the screening surveys, in contrast to a report from a hospital-based study⁵⁶. Hypertension is associated with a mildly increased risk of AAA. Diabetes and hypercholesterolaemia are not

Table 6 Risk factors for abdominal aortic aneurysm

Risk factor	References	Relative risk
Male sex	22, 27, 31	6.5 (5.9–7.2)
Smoking	15, 16, 18, 28*, 31, 46, 61	2.9 (2.6–3.3)
Peripheral vascular disease	15, 18, 29, 31, 46	2.4 (2.0–2.9)
Cardiovascular disease	18, 28, 29, 31, 46, 65	2.2 (2.0–2.5)
Cerebrovascular disease	29, 31, 46	0.7 (0.6–1.0)
Hypertension	16, 18, 28, 31, 46, 61	1.5 (1.4–1.6)
Hypercholesterolaemia	28, 31, 75†	1.0 (0.8–1.2)
Diabetes mellitus	18, 28, 31	1.0 (0.8–1.2)

Values in parentheses are 95 per cent confidence intervals. Relative risks were calculated from published figures of population-based screening surveys. *Ex-smokers and patients with unknown smoking status were not calculated. †Patients selected from a pulmonary outpatient department

associated with increased risk in the population-based studies that considered these factors. This is in sharp contrast to the strongly positive association between these conditions and ischaemic heart disease^{76–78}.

Pathogenesis

The exact pathogenesis of abdominal aortic aneurysm has not been completely unravelled. It is clear, however, that it involves a series of known and unknown environmental factors acting over time. A constitutional predisposition to aortic dilatation seems to be important. It is not known exactly which genetic risk factors make a person prone to aortic wall dilatation.

The structural integrity of the aortic wall depends mainly on elastin and collagen^{79–81}. Elastolysis appears to be the primary event in aneurysm formation⁸². Destruction of elastin in the aortic wall may represent a key event that shifts the load caused by blood pressure on to collagen^{79,81}. With increasing elastolysis, becoming manifest in the widening of the aorta, collagen function may become an important determinant of aneurysm growth⁸³. Collagen, because of its structural properties, must also weaken or fail for substantial dilatation to occur.

The familial clustering of AAA suggests a genetic basis, but the precise mode of inheritance is still disputed^{50,84,85}. Genetic variation in the elastin gene is thought to be negligible and has not been demonstrated in patients with AAA⁸¹. Several candidate genes, including the structural genes for the collagen I, II, III, V and VI gene family and their modifying enzymes, are under investigation^{86,87}. Genetic variation in type III collagen has been shown to affect the distensibility of the aorta⁸⁸. Diseases like Ehlers–Danlos type IV (characterized by a deficiency of type III collagen and in which spontaneous aortic rupture occurs) provide evidence of a central role of collagen in aortic aneurysmal disease. An association between AAA and inguinal hernia and chronic obstructive lung disease has been reported^{41,63,75,89}. It is still unclear whether the genetic basis of aneurysm formation in the general population is increased degradation of structurally normal collagen, primarily due to increased levels of environmental exposure, or whether it is due to increased degradation of an inferior type of collagen in a predisposed segment of the population.

The environmental exposures associated with AAA are to an extent similar to those associated with other mani-

festations of atherosclerosis. Patients with peripheral vascular disease and those with manifestations of coronary atherosclerosis are at increased risk of developing an AAA. Yet the long held view that aneurysms are of atherosclerotic origin is being questioned⁹⁰. One reason is the distinctive epidemiology of aortic aneurysms compared with other forms of vascular disease^{37,69,91,92}. Mortality rates associated with AAA are not declining, in sharp contrast to substantial decreases in mortality rates for cerebrovascular and cardiovascular disease⁹³. Another reason is that the risk factors for cardiovascular disease do not match exactly the risk factors for aneurysm formation. Hypertension seems to be more positively associated with coronary heart disease and cerebrovascular disease than with aneurysm formation. Hypercholesterolaemia and diabetes do not generally constitute an increased risk of AAA in contrast to the clearly increased risk of coronary heart disease and peripheral vascular disease. In summary, apart from the well known risk factor of smoking, very little is known about other environmental factors linked to aneurysm formation.

Prognosis

The risk of rupture of an AAA depends mainly on the size of the lesion or an increase in size of the lesion⁹⁴⁻⁹⁷. Aneurysms of less than 50 mm diameter rarely rupture^{94-96,98}. The reported annual rupture rate varies from 2.5 to 10 per cent, depending on the initial size of the aneurysm^{95,96,98,99}. The prognosis of aneurysms not operated on is less well known. Estimates from historical series and series of patients unfit for surgery show that life expectancy of patients with AAA is shortened without surgery. The 5-year survival of patients with aneurysms of more than 50 mm diameter who are not operated on is around 20 per cent^{95,100,101}.

Reports of life expectancy after a successful aneurysm repair vary. A Norwegian study found that the 10-year survival rate for all patients after operation was 38 per cent, compared with an expected 52 per cent. The standardized mortality rate was 1.30, indicating a 30 per cent higher mortality rate than in a demographically matched population. Older patients and patients with known cardiac disease have a significantly increased operative mortality rate¹⁰². A Canadian study¹⁰³ came to similar conclusions, showing that the late survival rate of patients with AAA is significantly less than that of an age- and sex-matched normal population (60.2 *versus* 79.2 per cent). After an aneurysm repair, late deaths from cardiac-related causes (44.4 *versus* 34.1 per cent) and cerebrovascular causes (8.3 *versus* 5.8 per cent) were more frequent. However, aneurysm formation is generally associated with smoking, coronary heart disease and an increased risk of chronic obstructive lung disease. So patients who undergo an aneurysm repair tend to be less healthy than the normal population. An American study⁴ concluded that the overall survival experience of patients after an aneurysm repair compared well with overall male life expectancy in the USA, if adjusted for the increased co-morbidity.

Prevention

Primary prevention of AAA is the prevention of any dilatation of the abdominal aorta. This does not seem to be achievable in the short term. Of the risk factors significantly associated with an increased risk of AAA, only

smoking is amenable to intervention and there is a time lag of about 40 years between increasing cigarette consumption and increasing mortality rate from aortic aneurysm in England and Wales⁷⁹. In view of the slow reduction in cigarette consumption¹⁰⁴ and the big time lag, any tangible impact on the incidence of aortic aneurysm as a result of the reduction in cigarette consumption is unlikely in the short term. More information is needed about other risk factors associated with aneurysm formation before public health measures to reduce the risk of AAA can be considered.

Secondary prevention, defined as taking measures for early detection followed by effective intervention to correct departures from good health, seems the only realistic option at the moment. Screening by ultrasonography is a cheap and reliable way of detecting AAA at an early stage^{20,105,106}. The only effective intervention to 'correct departures from good health' is an elective repair of the asymptomatic lesion, but still this involves a major operation with an associated mortality rate. Any intervention that would avoid this drawback would make secondary prevention much more attractive. A medical treatment to prevent growth of small aneurysms would add to the benefits of a screening programme, especially since the vast majority of screen-detected aneurysms are small.

Medical treatment to prevent aneurysm growth

Risk factors, such as diabetes, hypertension and hypercholesterolaemia, are not associated with a significant increased risk of AAA. Treatment of these factors will have negligible impact on the growth of small aneurysms. The other available options are modulation of inflammatory aneurysms or treatment of elastin or collagen abnormalities.

Some 4-10 per cent of all aneurysms are of inflammatory origin^{1,81} and inflammatory phenomena have been linked with accelerated growth in a rodent model. In 80 per cent of non-inflammatory aneurysms an inflammatory infiltrate is found, but this is thought to be a secondary phenomenon. A recent case series suggested that long-term steroid treatment accelerates the formation of aortic aneurysm, with a high risk of rupture¹⁰⁷; this has been confirmed in the blotchy mouse animal model¹⁰⁸. Anti-inflammatory medication in the form of steroids is not indicated in the treatment of inflammatory aneurysm.

Beta-blockers have an established place in the treatment of aortic dissection¹⁰⁹. Propranolol prevents or delays the formation of aortic aneurysm in the broad breasted turkey and the blotchy mouse animal models^{110,111}. Propranolol lowers the heart rate and the rate of arterial pressure rise and raises the tensile strength of the aortic wall in the turkey model. Increasing the plasma propranolol level produces no additional haemodynamic changes but causes a significant increase in the tensile strength of the tissues, which is partially due to increased intermolecular cross-links of collagen in the aortic wall¹¹². In the blotchy mouse model, propranolol treatment results in decreased solubility of dermal connective tissue, suggesting a direct effect of propranolol on connective tissue metabolism. In the hypertensive rat model, propranolol reduces the size of experimental AAAs, independently of the dose and by a mechanism that may be unrelated to simple blood pressure reduction¹¹³.

In a small retrospective study¹¹⁴ of 27 patients with an AAA who were initially treated non-operatively, 12

receiving long-term beta-blockade were compared with 15 controls. Among patients with beta-blockade, the mean aneurysm growth was 1.7 mm per year, compared with 4.4 mm per year in the controls. Of the patients receiving beta-blockade, half took the non-selective beta 1/beta 2-antagonist propranolol while the remainder received one of the more selective beta 1-antagonists. A larger study¹¹⁵ measured the growth of aneurysms in 121 patients treated without an operation. Eighty-three patients received no beta-blocker and 38 received beta-blockers. The mean(s.e.m.) growth rate in the latter group was 3.0(3.9) mm per year, compared with 4.4(4.2) mm per year in the control group; this was not statistically significant. A subgroup of 34 patients with an AAA larger than 50 mm who were unsuitable for surgery were analysed separately. Data presented in a graph indicated a statistically significant reduction in the growth rate of AAAs in those taking beta-blockers. Exact figures for growth rate in both groups, numbers of patients and length of follow-up were not reported.

The only randomized trial of propranolol and aortic dilatation involved 70 patients with Marfan's syndrome¹¹⁶. Those patients treated with propranolol had significantly lower rates of aortic dilatation than controls, and fewer patients reached a predetermined endpoint for withdrawal from the study. A partly retrospective study reported that atenolol also significantly reduces the rate of aortic root dilatation in patients with Marfan's syndrome¹¹⁷.

Randomized controlled trials of propranolol in patients with small AAA have been started in Huntingdon, UK and Denmark. In Huntingdon, the mean growth rate in the whole group of patients with a small aneurysm was 1.5 mm per year, which is comparable to the growth rate in other screening studies in the UK. This growth rate is considerably less than the average growth rates reported in the three propranolol studies. The rate of those three studies may overestimate the mean rate of aneurysm growth in the population, because the patients were recruited from a population which was unsuitable for surgery and had larger initial aortic diameters. The results of the randomized propranolol trials are not expected to be published before 1998.

In conclusion, there seems to be little evidence for the efficacy of medical treatment for AAA. The only promising addition to surgery for small AAAs may be propranolol. Until the results of randomized controlled trials become available, the only sensible prevention for ruptured aneurysm is elective surgery for asymptomatic lesions over a certain size.

Screening with elective repair of asymptomatic aneurysms

There is an ongoing debate over the merits of screening for asymptomatic AAA^{14,118-122}. Some authors are in favour of screening^{14,118,121,123}, while others conclude that a screening programme cannot be justified^{119,120,122}. All have in common a reliance on assumptions based on literature data. A screening programme can be justified if two main criteria are met. First, such a programme should be effective in reducing death or disability from a disease; second, it should be cost effective. So far two reports have been published which examine the influence of screening on the incidence of ruptured AAA in an actual screening project. Both studies concluded that the incidence of ruptured AAA was reduced by over 50 per cent in the group invited for screening^{22,124}. These reports suggest that

screening is effective in reducing ruptured AAA. A national trial of screening for asymptomatic lesions in the UK, funded by the Medical Research Council, has now started.

Clear answers on the second question of cost effectiveness have not been provided. Cost effectiveness comparisons can be made through 'cost per life-year saved' calculations or via an estimate of 'number needed to treat to save one life'. Cost per life-year saved calculations have the disadvantage that they are sensitive to local health care costs; number needed to treat analyses do not suffer from this drawback. Comparisons by number needed to treat between different health intervention programmes tend to be more robust and they can also be used between different countries. Reports of a cost-utility analysis of screening based on data from an actual screening project have not been published to the authors' knowledge. Two cost-utility studies using data from the literature and costs based on the British National Health Service concluded that the cost per life-year gained was between £746 and £1500 (refs 121, 123). This compares favourably with the calculated costs for breast cancer screening^{125,126}.

Evidence is becoming available that screening is effective in reducing the incidence of ruptured AAA. Studies based on literature data suggest that aneurysm screening could be cost effective compared with screening for other types of disease. This contrasts with the lack of data about the size of aneurysm at which intervention is most cost efficient. An important 'cost' aspect of screening is the mortality rate associated with elective repair of asymptomatic lesions. An operation for an asymptomatic aneurysm is indicated if the mortality rate associated with elective repair is lower than the risk of rupture. Setting the intervention criterion too high risks losing lives owing to rupture occurring at small size, while setting the intervention criterion too low risks losing lives because of the mortality rate associated with elective repair in those whose aneurysm might never rupture. The risk of rupture of an aneurysm depends mainly on its size. Only scarce information, however, is available about the exact rupture risk of aneurysms of a certain size⁹⁴⁻⁹⁷. It has been stated that lesions of less than 50 mm rarely rupture⁹⁴, but a recent series of ruptured AAAs contained a small but significant proportion of ruptures in lesions of less than 50 mm¹³. Diameter criteria for operation on an asymptomatic aneurysm vary from 40 to 60 mm^{24,127,128}; more information is necessary to determine at what size precisely intervention is most beneficial. Some of this information will come from two current randomized trials set up to determine whether early surgery or ultrasonographic surveillance is the better management for small AAA^{129,130}, but a detailed study examining the cost effectiveness of intervention at different sizes is still needed.

Conclusion

Aneurysm of the abdominal aorta is an increasing health problem. Trends in incidence and mortality data point to an increase in incidence of AAA. There is a vast difference between the mortality rates of operations for ruptured aneurysms and these for elective repair of asymptomatic lesions. Since the mortality rate associated with repair of an asymptomatic lesion is not negligible, surgery should be offered to those in whom the risk of rupture exceeds the risk of surgery. Screening for asymptomatic AAA can reduce the incidence of rupture

by more than half. However, insufficient information exists about the risk of rupture in specific patients and the factors related to the prognosis of screen-detected aneurysms. A national trial of screening for asymptomatic AAA has commenced in the UK and should provide some answers. Further studies are needed to determine the costs effectiveness of screening for asymptomatic lesions, compared with that for other diseases. Studies are also needed to examine the effectiveness of different treatment strategies for screen-detected AAA.

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Digest

For a previous quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert selected the best from the April to June 1997 issues of *Der Chirurg*. A digest for

the *BJS* for the same period, which was written by Mr Colin Johnson, appeared in the German journal.

The April issue is traditionally dedicated to the Annual Meeting of the German Surgical Society. The Editorial of the Society's President addresses efficiency and economics in surgery and calls for active participation of surgeons in the discussion and resolution of these issues¹. The April issue also carries review articles on incisional hernia^{2–4} and imaging techniques in visceral surgery^{5–8}, while the reviews of May and June cover plastic surgery^{9–11} and nutritional support in surgical patients^{12–15}.

Chronic pancreatitis

Surgical treatment of chronic pancreatitis is mainly indicated to relieve pain, but in some of these patients the risk of cancer or complications involving the duodenum and/or common bile duct may favour the decision to resort to operative treatment. Drainage and resection and any combination thereof have all been tried for these patients. Presently duodenum-preserving resection of the head of the pancreas (DPR) according to Beger, and limited resection of the pancreatic head combined with pancreatic duct drainage by longitudinal pancreaticojejunostomy (LP) as described by Frey may be considered to head the competition, the latter procedure being slightly easier to perform.

Both operations were compared within the framework of a prospective, randomized controlled trial regarding perioperative complications, pancreatic function, pain relief and overall quality of life¹⁶. Inclusion criteria were inflammatory tumour of the head of the pancreas larger than 35 mm, severe attacks of recurrent pain for more than 1 year or complications involving neighbouring organs. Since 1992, patients fulfilling the above criteria were randomized to either DPR ($n = 38$) or LP ($n = 36$). Mean(s.d.) operative time was 315(91) min for DPR and 284(79) min for LP (P not significant) and the mean(s.d.) number of units of transfused blood was 3.4(1.8) and 1.7(1.0) respectively ($P < 0.05$). Twelve of 38 patients in the DPR group and eight of 36 who had LP suffered complications ($P < 0.05$). During a median follow-up of 30 (range 6–48) months 34 patients in the DPR group and 33 in the LP group remained pain free. Quality of life improved significantly compared with preoperative values, but without difference between operative procedures. In some patients deterioration of endocrine pancreatic function was recorded, but there was no significant difference when the two operations were compared. Approximately 70 per cent of patients were able to return to work and this correlates with the number of patients giving up alcohol abuse. The authors conclude that presently neither method can be considered superior and call for longer follow-up.

Outpatient laparoscopic cholecystectomy

Between July 1993 and March 1996 a total of 140 patients with gallstones were treated by laparoscopic cholecystectomy on an outpatient basis by a group in

Cologne¹⁷. To qualify for outpatient cholecystectomy patients had to fulfil the following criteria: symptomatic cholelithiasis, demonstration of stones in the gallbladder by abdominal ultrasonography, an American Society of Anesthesiologists (ASA) score of 1–2 (3) and provision of postoperative care at home.

Anaesthesia was induced as 'balanced anaesthesia' and continued as minimal flow anaesthesia. Anaesthesiological monitoring included pulse oximetry, muscle paralysis and capnography. After operation thrombosis prophylaxis with low molecular weight heparin and a one shot antibiotic prophylaxis was given. Postoperative surveillance ended when the patient was fully conscious, mobilized and in a stable circulatory condition. When leaving the hospital on the same day the patient received a written report of the operation and instructions regarding further treatment. The patient was also given four tablets of a medium-strength analgesic, and later in the evening was contacted by telephone and his or her condition was checked.

A total of 31 patients referred for ambulatory cholecystectomy did not meet the inclusion criteria. Ten patients had asymptomatic cholelithiasis, in five patients ultrasonography failed to detect stones, four were ASA grade 3–4 and in nine patients provision of postoperative care was deemed inadequate. Three patients felt insecure and refused ambulatory cholecystectomy.

The mean age of 140 operated patients was 46 years, the oldest patient being 84 years old. All operations could be completed laparoscopically with only one exception. In this patient a gallstone had penetrated into the greater omentum. The operation was converted to open cholecystectomy and this patient also was discharged on the day of the operation. Mean operative time was 42 (range 20–180) min and mean time of anaesthesia was 64 (range 38–210) min. There were no major postoperative complications. Eight and six patients respectively were recorded to have haematoma or serous secretion. Only one haematoma required evacuation. There was no incidence of infection or bile leakage. One patient developed a trocar-site hernia after 21 months. Patients were back to work after a mean of 13.1 (range 3–24) days. Some 10–14 days after operation all patients indicated that they would have the outpatient procedure again. The authors concluded that suitable patients can be selected for ambulatory day-case laparoscopic cholecystectomy and that this procedure can be performed with a low postoperative complication rate.

Gastric cancer

The British and the Dutch multicentre studies of lymphadenectomy for gastric carcinoma have recorded high postoperative morbidity and mortality rates following total gastrectomy. A German multicentre study on patients with gastric cancer was carried out in six academic hospitals between August 1991 and March 1994¹⁸. The aim of the study was to examine the effect of perioperative antibiotic decontamination of the gastrointestinal tract on anastomotic leak rates and thus to

reduce the overall cost of hospital treatment. Patients and surgeons were blinded as to the treatment given. In the study group decontamination was achieved by oral application of polymyxin B 100 mg, tobramycin 80 mg, vancomycin 125 mg and amphotericin B 500 mg. Treatment started 1 day before operation and was continued until the seventh postoperative day. Both the study group and the control group were given intravenous cefotaxime as two perioperative doses. For the cost analysis, patients who had received antibiotic medication according to the decontamination protocol ($n=90$) were compared with non-decontaminated patients ($n=103$). The oesophagojejunal leak rate was 10.6 per cent in control patients and 1 per cent in decontaminated patients ($P=0.006$; Fisher's exact test). Contrast studies revealed only one asymptomatic anastomotic leak. The frequency of chest infection ($P<0.02$) and the overall complication rate ($P<0.025$) were also significantly reduced in the decontaminated group. During the observation period nine patients in the control group (8.7 per cent) and three in the treated group (3 per cent) died. This difference was not significant.

Patients were followed for 42 days after operation and the cost of treatment was calculated for this period only. The factors considered for cost analysis were the price of drugs used for decontamination, intravenous antibiotics, reoperation, non-surgical intervention, hospital charges for treatment on general wards as well as intensive care wards, and the cost of rehabilitation. In the control group the average cost per patient was calculated as DM20000 compared with DM16200 for patients in the decontaminated group. This difference reflects the lower number of patients requiring intensive care treatment in the control group ($P<0.01$), fewer patients requiring intravenous antibiotics ($P<0.025$) and fewer patients requiring reoperation ($P<0.1$). The cost of antibiotic decontamination was calculated as DM400 per patient and was less than the additional cost incurred from anastomotic leaks (DM3800 per patient for the whole group of 103 patients). The authors conclude that decontamination of patients scheduled for gastrectomy is cost effective and may be considered for routine use.

Thoracic surgery

Thoracic surgery is addressed in a number of articles in the June issue. A number of different lymph node mapping systems have been proposed for lymph node dissection and staging in patients with lung cancer. The use of a reproducible mapping system is essential to allow precise determination of the tumour node metastasis (TNM) stage and comparison of results from different surgical centres. To evaluate the current practice of lymph node mapping among thoracic surgeons in Germany, a mail survey was conducted¹⁹. A total of 90 hospitals performing thoracic surgery for lung cancer were approached and responses were received from 61 units (68 per cent). At present the majority of hospitals use the staging system suggested by the German Society for Thoracic, Cardiac and Vascular Surgery/Pneumology. Twenty-three per cent of hospitals use the system proposed by Naruke and another 25 per cent use a more individual form of lymph node recording. The number of dissected and examined lymph nodes is reported in 75 per cent of departments and the ratio of involved to resected nodes is reported by one in three departments. More than

half of the hospitals (59 per cent) indicated that mediastinal lymph node sampling was guided by the macroscopic appearance of lymph nodes, whereas 41 per cent of departments performed systematic *en bloc* resection of mediastinal nodes. It is of note that one in six departments indicated that contralateral lymph nodes were never sampled. The authors call for standardization of the methods of surgical lymph node sampling, pathological examination and reporting.

A precise autopsy study of lymph nodes was performed in 50 patients to determine the frequency of skip metastases in patients with malignant lung tumours (25 small cell lung cancers, 17 squamous cell carcinomas and eight adenocarcinomas)²⁰. A total of 1200 intrapulmonary, hilar, mediastinal or cervical lymph nodes were examined and lymph node metastases were demonstrable in 90 per cent of patients. Intrapulmonary and hilar nodes (N_1) harboured metastases in 82 per cent of patients, while 76 per cent of patients were found to have mediastinal lymph node metastases. Contralateral lymph nodes were positive in 18 of 25 patients with small cell carcinoma and in 12 of 25 patients with non-small cell carcinoma. Lymph node skipping defined as tumour-free lymph nodes in the course of the presumed metastatic pathway was recorded in 46 per cent of patients. Diligent examination of non-metastatic nodes showed that a substantial number of skipped nodes was affected by a variety of non-malignant pathological changes such as anthrasicosis, post-tuberculous alterations or radiation-induced fibrosis, whereas other skipped lymph nodes showed undiseased lymphatic tissue. The authors conclude that skip metastases are frequent in patients with malignant lung tumours. Although lymph node metastases were never found in nodes with complete hyalinization, no single pathological mechanism could be identified to explain the phenomenon of skip metastases.

Achilles tendon rupture

Non-operative treatment of Achilles tendon rupture is thought to be accompanied by a long period of immobilization and a high rate of rerupture. The current mainstay of treatment, therefore, is operative suture of the ruptured Achilles tendon. Ultrasonography, however, allows selection of patients who may benefit from a conservative approach. In the study from Bochum²¹, conservative treatment was chosen when ultrasonography in 20° plantar flexion indicated a distance between the proximal and the distal tendon stump of less than 5 mm. Since 1991, 23 patients meeting this condition were managed by immobilization for 1 week in 20° plantar flexion. After 1 week, patients were mobilized wearing special shoes with 3-cm heel pads. At night a special splint was applied. After 6 weeks the heel pad was reduced to 2 cm and after 12 weeks to 1 cm. Twenty-eight patients were managed surgically. The follow-up of 51 patients was 2.4 years. Minor wound infections after operative treatment were recorded in three of 28 patients, while rerupture was reported for three of 23 patients treated conservatively. Achillodynia was significantly more frequent in the conservative group. In the operated group mean isokinetic muscle strength was 14 per cent lower than in the uninvolved leg and decreased significantly with operative treatment to 75 per cent. The authors, there-

fore, recommend surgical treatment for acute Achilles tendon rupture.

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Digest

This second digest from Professor Christian Herfarth and Dr Thomas Lehnert covers articles from the July to September 1997 issues of *Der Chirurg*. A digest for the

BJS for the same period, again written by Mr Colin Johnson, appears in the German journal.

Reviews

This quarter's reviews comprise a series of articles on pathophysiology and surgical treatment of chronic pancreatitis^{1–4}, and perioperative risk in patients with associated disease^{5–12}.

Intraoperative cholangiography

In the times when cholecystectomy was performed as an open procedure many surgeons in training were taught that no cholecystectomy was complete without intraoperative direct cholangiography to ascertain that bile ducts were free from stones. With the advent of laparoscopic techniques intraoperative cholangiography became more difficult to perform and many surgeons felt it was not worth the additional effort. In agreement with previous randomized trials they argued that intraoperative cholangiography should be used selectively.

Two study groups from Marburg, Germany, and St Gallen, Switzerland, have combined their efforts and performed a prospective, randomized trial in which the efficacy of routine intraoperative direct cholangiography during open or laparoscopic cholecystectomy was examined¹³. Between July 1993 and March 1995 a total of 275 patients were entered into the trial. Patients were excluded if they had clinical signs of cholestasis during the past 6 months, if alkaline phosphatase, bilirubin, aspartatamino transferase, alaninamino transferase or serum amylase levels were raised, or if ultrasonography demonstrated stones in the common duct or a duct diameter of 6 mm or more. If endoscopic retrograde cholangiopancreatography (ERCP) or intravenous cholangiography had been performed during the past 6 months patients were also excluded. Randomization was performed by opening sealed envelopes deposited in the operating room immediately before the start of the operation. At 12 months after operation patients were asked to visit the outpatient clinic for a final evaluation of postoperative signs and symptoms of biliary disease.

Eight of 138 patients randomized to cholangiography had conventional operations compared with five of 137 patients in the no-cholangiography group. Mean(s.d.) operating time was significantly longer for the cholangiography group (92(31) versus 77(28) min; $P < 0.01$). In 27 (19.6 per cent) of 138 patients allocated to intraoperative cholangiography this was not possible. The frequency of postoperative complications was 7.2 per cent in the cholangiography group versus 5.8 per cent in the no-cholangiography group. When cholangiography was performed, four patients were thought to harbour stones in the common bile duct or in the cystic duct. In three patients this was confirmed and stones were successfully removed endoscopically, but in one patient no stone was demonstrable on ERCP and this was considered a false-positive result of intraoperative cholangiography. During the 12-month postoperative follow-up three patients in

the no-cholangiography group ($n = 137$) passed a common duct stone and in one patient a common duct stone was removed endoscopically. One other patient had an episode of acute pancreatitis which may have been due to a retained stone although this was not proved. The authors conclude that routine intraoperative cholangiography is not warranted when patients with suspected stones before operation are referred for endoscopic papillotomy and bile duct clearance.

Access for laparoscopy

While laparoscopy is commended for providing gentle access to abdominal operations, the optimal method of access for laparoscopy has not been determined. Traditionally pneumoperitoneum is established by abdominal puncture with a Veress needle and insufflation of gas before the first trocar and cannula is inserted. For patients with previous abdominal operations an open technique to insert laparoscopic instruments has been preferred. The latter approach is considered safe and may have economic advantages since it allows exclusive use of non-disposable instruments. However, gas leak has been feared when the open technique is employed. In a prospective, controlled and randomized study, open access to laparoscopy was compared with the traditional Veress needle puncture technique¹⁴. Between July and November 1996 a total of 50 patients were randomized to either open access port insertion or to the Veress needle technique. Indications for laparoscopy were cholecystectomy ($n = 18$), diagnostic staging laparoscopy ($n = 12$), gastrotomy ($n = 9$), splenectomy ($n = 6$) and a small number of other procedures. During the recruitment period 14 patients with previous abdominal surgery had to be excluded from the trial. Mean(s.d.) age of the 29 men and 21 women was 52.5(2.7) (range 21–89) years. Twenty-four patients were randomized to needle puncture and 26 patients were allocated to the open access group. Needle puncture required more attempts at proper placement than open access (mean(s.d.) 1.6(0.2) versus 1). The total number of cannulas used was similar in both groups (3.5 per patient), but in the open access group significantly fewer disposable instruments were needed (mean(s.d.) 0.2(0.1) versus 1.2(0.1); $P < 0.01$). Overall, operating time was shorter when the open access route was used compared with needle puncture (mean(s.d.) 52(8) versus 62(12) min). There were no access-related complications in either group, but two conversions were necessary because needle puncture did not provide reliable access to the peritoneal cavity in two patients. The authors conclude that in this small study there was very little difference between the two techniques. They speculate that very much larger trials including some 10 000 patients would be required to identify statistically significant differences and that such studies could only be performed as multicentre trials. They recommend the open access route for its economic advantages.

Robotics in laparoscopic surgery

Tired surgical assistants represent a well known, but for a variety of reasons widely ignored, phenomenon. This may be particularly bothersome, if it is the assistant's responsibility to guide the optical instrument in laparoscopic procedures such as cholecystectomy. Some surgeons have expressly wished that they were able to assist themselves. This wish may now come true. An American company has now introduced a voice-controlled robotic arm suitable for leading the optical instrument in laparoscopic cholecystectomy. Baca¹⁵ from Bremen reports on the use of this robot arm in 52 operations, of which 29 were performed as solo surgery with only the help of the robot arm. The arm is mounted to the operating table in approximately 5 min after some practice. Voice recognition is highly sophisticated. For each individual surgeon a chip card is loaded with a total of 23 commands which have to be repeated three times. This individual chip card is inserted into the main computer immediately before the operation. During the operation commands are relayed to the robot arm via a head microphone. Normal conversation during the operation is not impaired, since only single commands are recognized by the computer module. Fifty-two operations were performed with highly satisfactory voice recognition. The author considers use of the robot arm to control the video-optic instrument during laparoscopic surgery to be very useful, not least because the number of surgeons required for a procedure can be reduced.

Preoperative coagulation studies

Preoperative testing for coagulation disorders is a standard procedure before major surgical interventions. Luckily the vast majority of patients have normal coagulation parameters. In times of economic restrictions it is reasonable to ask just how much testing is required to detect the few patients with disturbed coagulation. The group from Marburg has addressed this issue and retrospectively studied 1447 patients scheduled for major abdominal or thoracic surgery between 1 January and 31 December 1991 at the Department of General Surgery, University of Marburg¹⁶. Screening for coagulation disorders included obtaining a detailed history, platelet count, prothrombin time (PT) and activated partial thrombin time (aPTT). Platelet counts less than 150 000 per ml, PT less than 70 per cent or a PTT exceeding 38 s were considered pathological. Risk factors studied included a history of hepatobiliary disease (cirrhosis, hepatitis, jaundice due to biliary occlusion), anti-coagulation treatment with warfarin or aspirin during the past 5 days or perioperative heparin treatment, renal insufficiency or a history of increased bleeding in the past. Bleeding complications included all episodes of bleeding requiring specific treatment (e.g. operative revision, drainage of haematoma or pressure bandages). A history indicating an increased risk of postoperative bleeding was recorded in 439 patients, mostly due to anticoagulation treatment with heparin ($n=328$), and 26 (5.9 per cent) of these patients developed a complication. Some 176 (12.2 per cent) of the patients had pathological laboratory tests. Postoperative bleeding was observed in 11 patients (6.3 per cent). The sensitivity of all three coagulation parameters in combination was 23.9 per cent and specificity was 88.2 per cent. Positive and negative predictive values for the development of postoperative

bleeding complications were 6.3 and 97.2 per cent respectively. In contrast the sensitivity of a history indicating an increased risk was 56.5 per cent. Pathological coagulation parameters were found almost exclusively in patients at risk of bleeding, whereas most patients (75 per cent) with bleeding complications had normal laboratory screening tests. The authors conclude that screening tests alone are insufficient to detect patients with an increased risk of bleeding. A detailed history should be taken and if it indicates an increased risk detailed laboratory studies to identify the precise cause of the bleeding disorder should follow.

Postoperative personal hygiene

'When can I take a shower?' was probably one of the questions most frequently asked by patients after operation in the hot days of the past summer. Riederer and Inderbitzi¹⁷ from Switzerland have tackled the problem seriously. They report the successful completion of a prospective, randomized and controlled trial in which patients were allocated to the treatment or control group in an alternating fashion. All patients operated for inguinal hernia during a 16-month period were asked to participate. Patients in one group were allowed to take a shower without wound dressing from the first post-operative day ($n=49$), whereas patients in the other group were not allowed to shower for 14 days after operation ($n=52$). Twenty patients were excluded after operation; in 15 patients a wound drain was inserted and five patients refused participation.

In the 'early shower' group up to 80 per cent of patients took a shower during the first 5 days after operation, while 18 of 101 patients indicated they did not care whether they had the opportunity to take a shower or not. No subcutaneous wound infection was recorded in any patient in either group. The authors conclude that a daily shower in the early postoperative period will not jeopardize wound healing, but this may be beneficial for personal hygiene.

In an invited commentary, Professor Daschner¹⁸ from Freiburg, a notoriously outspoken man when it comes to hospital hygiene, commends the authors for their fine study, but points out that personal soap bars may be severely contaminated and emphasizes the use of liquid soap instead. He also reminds us that early wound contact with potentially contaminated tap water may also be undesirable in immunocompromised patients, e.g. after organ transplantation.

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Digest

Dr Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the July to September 1997 issues of his journal for this

quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Oesophageal surgery

A total of 28 colon oesophageal replacements performed in children for long gap oesophageal atresia (22 patients) and intractable caustic stricture (six patients) were reviewed¹. Emphasis was placed on identifying the pros and cons of the different reconstruction techniques: intrathoracic route (ITR; 19 patients) and retrosternal route (RSR; nine patients). No hospital deaths occurred, but there was a higher morbidity rate among patients operated on using the ITR as opposed to the RSR (13 of 19 versus five of nine, *P* not significant). Six patients developed an anastomotic fistula (four with the ITR and two with the RSR, *P* not significant), whereas an anastomotic stenosis occurred in 13 patients (six of nine with the RSR and seven of 19 with the ITR, *P* < 0.07). Overall, dysphagia was the most prevalent symptom at 3 months' follow-up, but had significantly decreased at the final follow-up (14 of 26 versus four of 25; *P* < 0.0027). Functional results improved significantly during follow-up (score 1–2 versus 3–4; *P* = 0.001, Fisher test). However, despite the higher morbidity rate, better functional results were achieved using the ITR as opposed to the RSR.

The expression of bcl-2 protein in oesophageal squamous cell carcinoma (SCC) and basaloid carcinoma (BC) was examined immunohistochemically, and its relation to tumour progression and postoperative survival was determined in SCC². A total of 42 SCC and four BC tumour samples were fixed with formalin, embedded in paraffin and stained using monoclonal bcl-2 protein antibody, clone 124. Immunoreactivity was scored semiquantitatively, and the staining results were compared with the pathological features and survival rates. The cytoplasm of basal cells from normal oesophageal epithelium was stained. In some well and moderately differentiated SCCs bcl-2 protein-positive reaction was observed in the peripheral part of the tumour cord, but in poorly differentiated SCC the cells were weakly or not stained. However, in BC the cells were strongly stained. There was positive immunoreactivity in 19 of the 42 SCCs and all of the BCs. There were no significant differences in pathological features or patient survival between the bcl-2 protein-positive and protein-negative SCCs. In conclusion, the expression of bcl-2 was not related to tumour progression and had no prognostic significance in SCC. Conversely, BC had strong immunohistochemical expression, probably associated with the differentiation of carcinoma cells simulating the basal cells of the oesophagus.

Gastric surgery

An experimental study was conducted using a canine model to elucidate whether the transected vagus nerve can be anastomosed conveniently, and to determine when and to what degree the vagorrrhaphy retains its functions³. In the vagorrrhaphy group (*n* = 5), the anterior and posterior vagal trunks were transected 1.5 cm above the diaphragm and the cut ends were anastomosed using two

stitches of 8/0 nylon and fibrin glue adhesive without microsurgery. In the non-vagorrrhaphy group (*n* = 5), a 1-cm length of the nerve segment was resected to prevent reinnervation. A microscopic study of the anastomotic site performed on postoperative day 10 indicated the interruption of nerve fibres between the cut ends. No differences were found in gastric secretory function, as assessed by the Hollander insulin test, or in emptying function, as assessed by the acetaminophen test, between the vagorrrhaphy group and the control preoperative values. However, both of these functions were superior in the vagorrrhaphy group compared with the non-vagorrrhaphy group. These results indicate that this technique of vagal anastomosis could be put to practical use in gastric cancer operations to avoid postvagotomy syndrome.

Nakane *et al.*⁴ modified the operative procedures used in pouch and interposition (PI) reconstruction in an attempt to improve the surgical results after total gastrectomy, because a randomized controlled trial had revealed that the clinical assessment of PI was quite poor, even though it is a physiological route. In most of the patients treated, the gastric emptying test revealed delayed emptying, and a radiographic video film showed folding and twisting of the jejunal conduit between the pouch and duodenum, which disturbed the transmission of nutrients. Modified PI (m-PI) was performed by decreasing the length of the jejunal conduit and widening the mesenteric pedicle to preserve the blood and nerve supply. This procedure was compared retrospectively with the PI reconstruction used previously by evaluating postprandial symptoms, food intake, body-weight, serum nutritional parameters, and emptying time of the gastric substitute. Patients in the m-PI group (*n* = 6) showed a lower incidence of symptoms, a greater food intake and a greater weight recovery than those in the PI group (*n* = 6). The gastric emptying test also revealed an acceptable degree of emptying. The authors conclude that the m-PI reconstruction is more useful for improving the quality of life after operation than the method of PI reconstruction used previously.

Colonic and rectal surgery

During pathological examination, cancer nodules, and not lymph node metastasis, are often seen in the fatty tissue outside the rectum⁵. The significance of this type of cancer spread, which is called extrabowel skipped cancer infiltration (EX), was investigated. A total of 369 patients who underwent resection of rectal adenocarcinoma between 1980 and 1992 were reviewed. All surgical specimens were examined microscopically to determine whether EX existed in the fatty tissue outside the rectum or in the detached fatty tissue around the dissected lymph nodes. The EX was divided into four patterns: scattering (sct), vessel invasion (ves), neural invasion (ni) and nodular (nd). EX was found in 130 patients (35.2 per cent). Of these, 19 were sct, 58 ves, 21 ni and 111 nd. The overall recurrence rate after curative resection was 52.8

per cent in the EX-positive group and 24.0 per cent in the EX-negative group ($P < 0.001$). The local recurrence rate was 35.8 and 14.9 per cent respectively ($P < 0.01$). The EX-positive group exhibited a significantly worse survival than the EX-negative group ($P < 0.001$). The presence of EX reflects the aggressive biological activity of rectal cancer. EX may be a significant prognostic predictor in these patients. Therefore, treatments such as extended dissection and postoperative adjuvant therapy, and meticulous follow-up, are all considered to be necessary for patients with EX.

The expression of E-cadherin was determined by immunohistochemical staining in tumour tissue and in adjacent normal mucosa taken from 100 resected specimens of colorectal carcinoma⁶. The expression of E-cadherin was preserved in all normal mucosa, but in the tumour tissue specimens it was preserved in 43, was heterogeneous in 32 and was lost in 25 samples. The absent or heterogeneous expression of E-cadherin correlated closely to an advanced clinical stage of colorectal cancer, advanced tumour penetration, undifferentiated tumour histology, widespread lymph node involvement, liver metastasis, and permeation into the lymphatic and venous channels. The lost or heterogeneous expression of E-cadherin in tumour tissue was also associated significantly with an increased incidence of tumour recurrence after apparently curative resection, a reduced overall survival rate and a reduced disease-free survival rate. Multivariate analysis disclosed that the expression of E-cadherin in tumour tissue was a significant prognostic variable independent of other clinicopathological features.

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Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies

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Background There is controversy over whether perioperative allogeneic red blood cell transfusions are associated with an increased risk of cancer recurrence, postoperative infection or death in patients with cancer undergoing surgery.

Methods A systematic meta-analysis was performed to answer this question. Studies were identified from electronic databases (Medline 1966–1997, Cancerlit 1983–1997, Current Contents, Cinahl 1982–1996, Healthstar 1990–1997, Bioabstracts 1990–1996 and Embase), by hand search of the bibliographies of identified studies and relevant journals, and by contact with experts in the field. All randomized controlled trials or prospective cohort studies with active comparator controls (autologous or leucocyte-depleted allogeneic blood) were eligible for inclusion if they reported on mortality, infection or recurrence rate in patients with cancer undergoing potentially curative surgical resection. The validity of the identified studies was assessed by means of a standardized scale, and data abstraction was carried out by two investigators independently. A random effects model was used for data synthesis.

Results Of the 2172 references identified, only 17 studies fulfilled the inclusion criteria. After exclusion of duplicate publications, six randomized controlled trials and two prospective cohort studies with appropriate concurrent controls were included in the analysis. The summary risk ratios were 0.95 (95 per cent confidence interval (c.i.) 0.79–1.15) for all-cause mortality and 1.06 (95 per cent c.i. 0.88–1.28) for cancer recurrence, the two endpoints that were appropriate to combine statistically. There was significant heterogeneity (explainable by differences in study design and patient characteristics) in the postoperative infection data and the summary risk ratio was 1.00 (95 per cent c.i. 0.76–1.32) for the four studies that were appropriate to subject to meta-analysis. Given the sample sizes of these eight studies, this meta-analysis had insufficient power to detect a relative difference of less than 20 per cent in the frequency of death, cancer recurrence or infection between the allogeneic and control transfusion arms.

Conclusion Although more studies are required before a definitive statement can be made, at this time there is no evidence that allogeneic blood transfusion increases the risk of clinically important adverse sequelae in patients with cancer undergoing surgery.

Neoplastic disease is the most common primary diagnosis in transfusion recipients and these patients receive nearly one-quarter of all transfused blood^{1,2}. In particular, blood transfusions are commonly^{2–5} administered to patients with cancer undergoing surgery. However, *in vitro*

studies^{6,7} have shown that natural killer cell activity is reduced and suppressor T cell activity is increased after exposure to allogeneic products, and allogeneic blood transfusion is associated with improved renal transplant survival⁸ and reduced severity of some autoimmune diseases⁹ in clinical studies. This suggests an immunosuppressive effect from allogeneic blood products and has led to concerns about the safety of this treatment, particularly in patients with cancer¹⁰, and to the suggestion that perioperative allogeneic blood transfusion may increase the risk of postoperative infection, recurrence and death in patients with cancer.

Although nearly 100 studies have been conducted over the past 15 years to investigate whether perioperative allogeneic blood transfusion is associated with adverse sequelae in patients with cancer, the results have been conflicting. In an effort to resolve the controversy, seven systematic overviews have been published in the past 6 years. However, they also have reported conflicting results, with four^{11–14} concluding that allogeneic transfusion is associated with an increased risk and three^{3,15,16} concluding that there is no excess risk. While these discordant results are discouraging, they are not surprising when the methods used in these overviews are looked at closely. For instance, the overviews differed

Possible duplicate publication: this article has identified a number of instances where two or more published articles relate to the same data set. The Editors have examined these cases involving the *Journal*, and have asked the Editors of other journals to comment. In one case, a Danish translation was published with the consent of the original Editor. In others, different research questions have been addressed. Not all cases have been examined fully, but, to date, no infringement of the rules on duplicate publication has been detected. Authors should be aware that systematic reviews of this type are likely to detect instances of duplicate publication, and the Editors will continue to publicize the names of those responsible if the *Journal* is involved. Our Instructions to Authors contain clear guidance on the submission of relevant material with any potential overlap with articles submitted for publication. Authors who follow this guidance are unlikely to suffer subsequent embarrassment.

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markedly in their search strategies and eligibility criteria, such that the number of studies included ranged from three to 71. Moreover, most of the overviews combined data from prospective and retrospective studies to obtain a single summary statistic, a debatable approach given that effect estimates from retrospective studies are often vastly different from those in prospective studies¹². Finally, the published overviews have generally compared outcomes in transfused patients with those in non-transfused patients, an analysis that tends to neglect the influence of confounding conditions^{17–19} that are associated with both an increased likelihood of transfusion and a worse prognosis. Therefore, these reviews cannot answer the real question of interest: does exposure to allogeneic blood at the time of operation increase the risk of adverse sequelae in patients with cancer?

Randomized controlled trials provide strong evidence for causation as they control for the effect of confounders through the equal distribution of prognostic factors (both known and unknown) between treatment groups²⁰. Thus, a clinical trial in which patients were randomly allocated to allogeneic transfusion or no transfusion would be the best way to determine the effects of perioperative allogeneic blood transfusion. However, it is accepted to be unethical to transfuse patients without medical indication or to withhold transfusion in those who need it. As the immunomodulatory effect of allogeneic blood appears to be white cell mediated^{21,22}, and leucocyte-depleted or autologous blood does not seem to induce significant immunosuppression^{23–25}, either would be suitable controls in a randomized trial assessing the effects of allogeneic blood. Moreover, prospective cohort studies comparing patients transfused with autologous blood with those who received allogeneic blood could also be used to define the effects of allogeneic blood if the two cohorts were concurrent, similar in demographic and clinical features at baseline, and if the decision to give allogeneic rather than autologous blood were based solely on logistic factors (such as geographic inaccessibility to an autologous predonation programme) rather than medical eligibility or clinical features of the patients.

To determine whether there is a true causal association between perioperative allogeneic blood transfusion and cancer recurrence, postoperative infection or death in patients with malignancy, a meta-analysis was conducted of all randomized controlled trials with active comparators (leucocyte-depleted or autologous blood) and prospective cohort studies with appropriate comparison groups (as defined above). As the adverse effects of allogeneic blood are considered to be due to immunomodulatory effects and there is no reason to expect these effects to be limited to any one type of cancer surgery, all patients with solid tumours undergoing potentially curative resection were evaluated.

Patients and methods

Searching for relevant studies

Electronic databases (Medline 1966–1997, Cancerlit 1983–1997, Current Contents, Cinahl 1982–1996, Healthstar 1990–1997, Bioabstracts 1990–1996 and Embase 1984–1997) were searched using a modification of the Cochrane Collaboration Medline search strategy. The search was restricted to human studies and used textword terms (blood transfusion\$, cancer, malignancy, infection\$, death\$ or mortality) and MeSH headings (blood transfusion (exp), neoplasms (exp), bacterial infections, mortality or death (exp)). A search was made for abstracts or letters as well as full manuscripts, and language restrictions were not

applied. Hand searches of the bibliographies of all identified studies and all issues of the journals *Transfusion*, *British Journal of Surgery*, *Lancet* and *New England Journal of Medicine* published between January 1995 and March 1997 (inclusive) were done to identify any studies missed by the literature searches. Finally, members of the International Study of Perioperative Transfusion Group were contacted to determine whether there were additional published or unpublished studies relevant to the study.

A search of the electronic databases, completed on 9 February 1997, identified 2168 citations; a further three citations were identified from the hand search of bibliographies, and one citation was identified from the journal hand search. Two of the investigators (F.A.McA. and H.D.C.) independently reviewed the titles and abstracts to identify any prospective studies or randomized trials that appeared to report on outcome in patients with cancer undergoing potentially curative surgery who had received perioperative transfusions. The full texts of all potentially relevant articles were obtained and reviewed by both investigators using prestandardized data abstraction forms.

Selection of studies

All studies reporting outcomes of perioperative (from 24 h before to 30 days after operation) blood transfusion were eligible for inclusion. As detailed above, only randomized clinical trials (with autologous blood transfusion or leucocyte-depleted packed cells as the control arm intervention) or prospective cohort studies with appropriate concurrent controls were eligible for inclusion. To be included, studies had to report on major outcomes (all-cause mortality, cancer recurrence or postoperative infection) in patients with localized malignancy undergoing elective potentially curative surgery. Studies of patients undergoing palliative or emergency surgery were excluded. Cancer recurrence was defined as local recurrence or metastatic disease and was accepted if the original investigators detected characteristic abnormalities on physical examination, radiography (chest radiography, ultrasonography, computed tomography or bone scan), histology or cytology. Postoperative infection was defined as occurring within the first 30 postoperative days and was accepted if the original investigators documented evidence of bacteraemia (on blood culture) or a specific septic focus, such as wound infection, urinary sepsis or pneumonia.

Validity assessment

The quality of randomized controlled trials was determined by means of the Jadad scale²⁶ and the quality of the cohort studies was assessed with a modification of the McMaster checklist²⁷. The Jadad scale was developed and validated as a means to provide quantitative estimates of the quality of clinical trials, and evaluates studies using a five-point scale concentrating on methods of randomization, double blinding and full disclosure of withdrawals or drop-outs. None of the studies in this field was double blind and the maximum score on the Jadad scale was thus only three. The McMaster checklist²⁷ was developed by expert consensus and consists of three sections to evaluate observational studies. The cohort studies were graded out of five using the criteria in the validity section of the checklist (presence of clearly identified comparison groups that were similar with respect to potential confounders, outcomes and exposures measured in the same way in both groups, follow-up sufficiently long and complete, correct temporal relationship and the presence of a dose–response gradient).

Data abstraction

Data recorded included cancer type and age of the patients, the time period of the study, the total number of patients and the number transfused, the all-cause mortality during the timeframe of the study, the cancer recurrence rate and the postoperative infection rate (as defined above). Data were abstracted from each study by two of the investigators (F.A.McA. and H.D.C.) independently and the interobserver agreement on the quality

score was determined. Any discrepancies were resolved by consensus or the judgement of a third investigator (PSW). Outcomes were assigned according to the intention-to-treat principle (in other words, outcomes were attributed to that group whether or not the patient was actually transfused). In cases where the outcome data for each of the study arms were unclear, the original investigators were contacted for clarification.

Statistical analysis

Analyses were performed using the Meta-Analyst 0.998 software (J. Lau, New England Medical Center, Boston, Massachusetts, USA). Risk ratios were determined for each of the eligible studies and Cochran's Q test was done to assess for heterogeneity in each outcome of interest. Statistically significant heterogeneity was assumed at $P < 0.10$. The studies were combined using both a random effects model (the DerSimonian and Laird method) and a fixed effects model (the Mantel-Haenszel method). A risk ratio of 1.0 suggests that there was no difference between treatment and control, a risk ratio of less than 1.0 suggests that fewer events occurred in the allogeneic transfusion group than in the control groups, and a risk ratio greater than 1.0 suggests that more events occurred in the allogeneic group than in controls. Sensitivity analyses, defined *a priori*, were conducted to look at the effects of study design, study quality, year of study completion and publication status on the summary risk ratios.

Results

Study selection and evaluation

Of the 2172 citations originally identified by the searching strategies, 46 were retrieved as they appeared potentially relevant. However, 29 of these studies were excluded after detailed evaluation as follows: one randomized trial that did not report any of the outcomes relevant to this meta-analysis²⁸, two randomized trials that did not include any patients with cancer^{29,30}, 20 prospective cohort studies that compared transfused with non-transfused patients^{31–50}, two prospective cohort studies with control groups inappropriate for the purposes of this analysis^{51,52} and four cohort studies that on closer examination were really retrospective^{53–56}. Of the randomized controlled trial reports eligible for inclusion, eight appeared to have been published in more than one journal and, as the data were virtually identical in the second (or subsequent) publications^{57–64}, the first study was used for analysis. In one case, outcomes from a single randomized trial were reported in two separate publications^{65,66} and both were included as

they described different outcomes. Disagreement among the reviewers regarding eligibility of the studies occurred on two occasions for a κ value of 0.91. Disagreement on the quality scores occurred on one occasion for a κ value of 0.78. All disagreements were resolved by consensus.

Studies included in the meta-analyses

Summary data from the six randomized trials^{25,65–70} and two prospective cohort studies^{71,72} eligible for this meta-analysis are presented in Table 1. The vast majority of the subjects had colorectal cancer and were in their seventh decade of life. Although Jensen *et al.*^{25,67} included patients with non-malignant conditions in their two trials, approximately four-fifths of patients had colorectal cancer and all data from the trials were included because it proved impossible to separate the results for patients with cancer, either from the presented data or after correspondence with the authors. Between 32 and 100 per cent of subjects in the eight studies were transfused.

Quantitative data synthesis

All-cause mortality. Five randomized clinical trials and one cohort study reported mortality endpoints (Table 2). There were no significant differences between the allogeneically transfused patients and control patients in any of the studies. The summary risk ratio was 0.95 (95 per cent confidence interval (c.i.) 0.79–1.15) for the six studies, suggesting that allogeneic transfusion was not associated with an increased mortality risk in these patients.

The Q statistic for heterogeneity was not significant ($Q = 4.70$, 5 d.f., $P > 0.45$) and the summary risk ratio calculated under the fixed effects model (0.95 (95 per cent c.i. 0.79–1.14)) was identical to that derived from the random effects model. These findings suggest that there was no allogeneic transfusion effect on total mortality under various conditions.

Cancer recurrence. Three randomized trials and two cohort studies reported cancer recurrence rates (Table 3). None of the five studies found a significant difference between the allogeneically transfused patients and

Table 1 Description of studies included in the meta-analysis

Reference	Time period of study	Quality score*	Control transfusion	Cancer type	Median age of subjects (years)	Total no. of subjects	No. of subjects transfused
Randomized controlled trials							
Jensen <i>et al.</i> ²⁵	1989–1990	3	Leucocyte depleted	Colorectal†	64	197	104
Heiss <i>et al.</i> ^{65,66}	1987–1991	2	Autologous	Colorectal	60	120	120
Busch <i>et al.</i> ⁶⁹	1986–1991	2	Autologous	Colorectal	67	475	280
Houbiers <i>et al.</i> ⁶⁸	1987–1990	3	Leucocyte depleted	Colorectal	69	697	446
Kajikawa <i>et al.</i> ⁷⁰	1991–1992	1	Autologous	Hepatoma	60	42	29
Jensen <i>et al.</i> ⁶⁷	1992–1995	3	Leucocyte depleted	Colorectal‡	66	589	260
Prospective cohort studies							
Ness <i>et al.</i> ⁷¹	1982–1986	4	Autologous	Prostate	59	309	273
Giurati <i>et al.</i> ⁷²	Not stated	3	Autologous	Cervical	47	103	33§

*The Jadad score was used for the randomized trials; the modified McMaster scale was used for the cohort studies; †77 per cent of patients had colorectal cancer (others had benign colorectal conditions); ‡81 per cent of patients had colorectal cancer (others had benign colorectal conditions); §patients were subdivided into four groups, but only two were relevant for comparison of autologous versus homologous blood products

controls. The summary risk ratio for the five studies was 1.06 (95 per cent c.i. 0.88–1.28), supporting the contention that allogeneic transfusion is not associated with an increased risk of cancer recurrence.

The Q statistic was not significant ($Q = 3.64$, 4 d.f., $P > 0.45$) and the summary risk ratio calculated using the fixed effects approach (1.07 (95 per cent c.i. 0.89–1.29)) was essentially identical to that obtained with a random effects model. As evident from Table 1, these studies had relatively homogeneous patient populations and the homogeneous effect sizes are not surprising.

Postoperative infection. While three randomized trials^{25,65,67} demonstrated an excess risk of postoperative infection in patients receiving allogeneic blood, the other

three^{68–70} failed to reveal statistically significant differences between the groups (Table 4). Although the summary risk ratio was 1.63 (95 per cent c.i. 0.94–2.82) for the six trials, suggesting that allogeneic transfusion is associated with an increased (but not statistically significant, $P = 0.08$) risk of postoperative infection in these patients, there was significant heterogeneity in the results (Q statistic for heterogeneity 35.97, 5 d.f., $P < 0.001$) and it could be argued that it is inappropriate to attempt to combine these studies. Closer analysis of the data reveals that virtually all the heterogeneity is attributable to two studies^{25,67} published by the same research group. As detailed in the Discussion, these two studies were sufficiently different from the others with respect to patient mix and study design to justify their exclusion in a

Table 2 All-cause mortality in the included studies

Reference	Allogeneic transfusion		Control transfusion		Risk ratio*
	No. of deaths	Total	No. of deaths	Total	
Randomized controlled trials					
Heiss <i>et al.</i> ⁶⁶	14	62	8	58	1.64 (0.74–3.61)
Busch <i>et al.</i> ⁶⁹	56	236	66	239	0.86 (0.63–1.17)
Houbiers <i>et al.</i> ⁶⁸	89	360	84	337	0.99 (0.77–1.28)
Kajikawa <i>et al.</i> ⁷⁰	0	21	1	21	0.33 (0.01–7.74)
Jensen <i>et al.</i> ⁶⁷	5	299	10	290	0.48 (0.17–1.40)
Subtotal	164	978	169	945	0.94 (0.76–1.16)
Cohort study					
Ness <i>et al.</i> ⁷¹	5	94	7	179	1.36 (0.44–4.17)
Total†	169 (16)	1072	176 (16)	1124	0.95 (0.79–1.15)

*Values are point estimate (95 per cent confidence interval); †values in parentheses are percentages

Table 3 Cancer recurrence in the included studies

Reference	Allogeneic transfusion		Control transfusion		Risk ratio*
	No. of recurrences	Total	No. of recurrences	Total	
Randomized controlled trials					
Heiss <i>et al.</i> ⁶⁶	15	52	8	48	1.73 (0.81–3.71)
Busch <i>et al.</i> ⁶⁹	54	216	51	207	1.01 (0.73–1.41)
Houbiers <i>et al.</i> ⁶⁸	91	360	87	337	0.98 (0.76–1.26)
Subtotal	160	628	146	592	1.03 (0.85–1.25)
Cohort studies					
Ness <i>et al.</i> ⁷¹	11	94	13	179	1.61 (0.75–3.46)
Giurati <i>et al.</i> ⁷²	1	21	0	22	3.14 (0.13–72.96)
Total†	172 (23)	743	159 (20)	793	1.06 (0.88–1.28)

*Values are point estimate (95 per cent confidence interval); †values in parentheses are percentages

Table 4 Postoperative infection in the included studies

Reference	Allogeneic transfusion		Control transfusion		Risk ratio*
	No. of infections	Total	No. of infections	Total	
Randomized controlled trials					
Jensen <i>et al.</i> ²⁵	17	56	1	48	14.57 (2.01–105.49)
Heiss <i>et al.</i> ⁶⁵	17	62	7	58	2.27 (1.02–5.08)
Busch <i>et al.</i> ⁶⁹	58	234	64	236	0.91 (0.67–1.24)
Houbiers <i>et al.</i> ⁶⁸	115	360	118	337	0.91 (0.74–1.12)
Kajikawa <i>et al.</i> ⁷⁰	2	18	1	11	1.22 (0.12–11.95)
Jensen <i>et al.</i> ⁶⁷	90	299	33	290	2.65 (1.84–3.81)
Total†	299 (29)	1029	224 (23)	980	1.63 (0.94–2.82)

*Values are point estimate (95 per cent confidence interval); †values in parentheses are percentages

subsequent meta-analysis of the postoperative infection data. As can be seen from Table 5, meta-analysis of the remaining four trials revealed a risk ratio for postoperative infection of 1.00 (95 per cent c.i. 0.76–1.32)). This analysis appears to be more appropriate given the non-significant Q test statistic ($Q=4.77$, 3 d.f., $P=0.20$) and the similarity of the effect estimate obtained using the fixed effects model (relative risk 0.97 (95 per cent c.i. 0.82–1.14)).

Table 5 Sensitivity analyses

Study characteristics	Total no. of patients	Relative risk in allogeneic group
Total mortality		
Cohort studies	273	1.36 (0.44–4.17)
Low-quality RCT*	637	1.00 (0.62–1.59)
High-quality RCT†	1286	0.84 (0.47–1.52)
All RCTs	1923	0.94 (0.76–1.16)
All studies	2196	0.95 (0.79–1.15)
Cancer recurrence		
Cohort studies	316	1.67 (0.80–3.51)
Low-quality RCT*	523	1.18 (0.74–1.89)
High-quality RCT†	697	0.98 (0.76–1.26)
All RCTs	1220	1.03 (0.85–1.25)
All studies	1536	1.06 (0.88–1.28)
Postoperative infection		
Low-quality RCT*	619	1.28 (0.64–2.59)
High-quality RCT†	1390	2.24 (0.80–6.25)
Non-Jensen RCT	1316	1.00 (0.76–1.32)
Jensen RCT	693	4.65 (0.96–22.43)
All RCTs	2009	1.63 (0.94–2.82)

RCT, randomized controlled trial *Trials that received fewer than three points on the Jadad scale; †trials that received scores of three or more on the Jadad scale

Sensitivity analysis. This confirmed the conclusion that perioperative blood transfusion has no effect on all-cause mortality or cancer recurrence (Table 5). Postoperative infection has been discussed above: after exclusion of atypical results from one group, there was no effect. Cumulative analysis showed no effect of time on the three outcome measures (Fig. 1).

Sample sizes and power of analyses. Owing to the small number and size of the eligible clinical trials, this meta-analysis is underpowered to detect small differences between the two comparison groups. Specifically, given α of 0.05 and the total observed sample sizes, the power of this meta-analysis for detecting 10 per cent relative increases in all-cause mortality, cancer recurrence or postoperative infection in the patients transfused with allogeneic blood was only 27, 27 and 39 per cent respectively. In fact, given the event rates in the control groups, the sample sizes necessary confidently to exclude (with a power of 90 per cent) a 10 per cent difference in the various endpoints were approximately 12 500 for all-cause mortality, 8800 for cancer recurrence and 4800 for postoperative infection. However, the power to detect relative increases of 20 per cent with allogeneic transfusion was 76 per cent for mortality, 76 per cent for cancer recurrence and 93 per cent for infection.

Discussion

Meta-analysis of six randomized trials and two prospective cohort studies with appropriate control groups failed to confirm the hypothesis that perioperative allogeneic blood transfusions are associated with an increased risk of postoperative infection, cancer recurrence or mortality

	Year	No. of patients
Total mortality	1986	273
	1990	970
	1991	1565
	1992	1607
	1995	2196
Cancer recurrence	1986	273
	1990	970
	1991	1493
	1993	1536
Postoperative infection	1990	801
	1991	1391
	1992	1420
	1995	2009

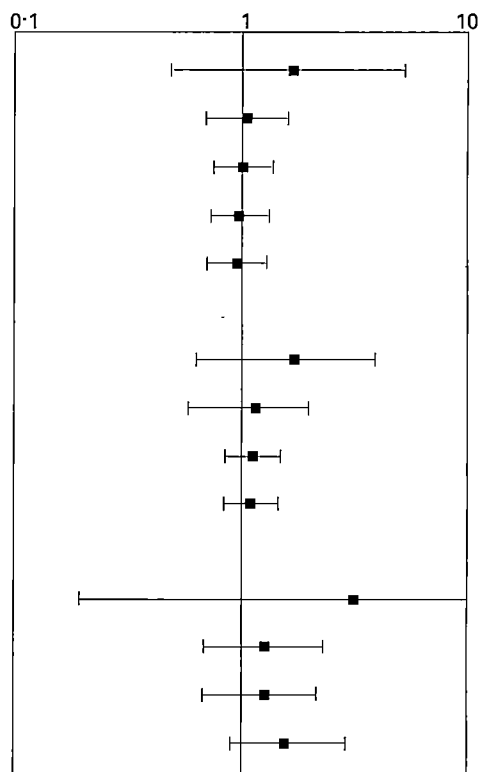


Fig. 1 Cumulative meta-analyses, by year of publication, for total mortality, cancer recurrence and postoperative infection. Values are point estimates of relative risk with 95 per cent confidence interval

in patients with cancer undergoing potentially curative surgery. While this meta-analysis is underpowered for detecting small differences, the data do suggest that the magnitude of any adverse effects on mortality, cancer recurrence or postoperative infection from allogeneic transfusion is less than 20 per cent.

The most important conclusion to emerge from this meta-analysis is the need for more (and larger) randomized controlled trials comparing allogeneic blood products with appropriate active comparators, such as autologous or leucocyte-depleted blood, in patients with cancer at the time of operation. While some may argue that a meta-analysis should be done only when there is a large quantity of data and the likelihood of a statistically significant treatment effect, the authors believe that meta-analyses have wider applicability. In the words of Goodman⁷³, meta-analyses can, and should 'raise research and editorial standards, by calling attention to the strengths and weaknesses of the body of research in an area'. As already pointed out, seven systematic overviews have been published on this topic in the past decade. However, this is one of only two overviews¹⁵ to employ strict inclusion criteria and the only one to highlight the paucity of evidence underlying claims about the hazardous effects of perioperative allogeneic blood transfusion. As a result of this analysis, the authors do not share recently expressed optimism⁷⁴ that a consensus conference and pooling of individual patient data from the published trials will be sufficient to determine whether there are adverse effects from perioperative allogeneic blood transfusion without the collection of more primary data.

There are a number of limitations with this meta-analysis. First, there were only eight studies, with a total of 2532 patients, and the largest study included only 697 patients (less than two-thirds of whom were transfused with either blood product). Any meta-analysis with small numbers has to be interpreted cautiously as small meta-analyses have been shown to provide effect estimates that differ significantly from those eventually found in large definitive randomized trials⁷⁵ (although small meta-analyses tend to overestimate the treatment effects). A second limitation is the inability to identify any unpublished studies in this area. While it seems reasonable to hypothesize that some studies have been missed (two were estimated by the capture-recapture method⁷⁶), it is unlikely that any unpublished studies would change the conclusions of this analysis because positive studies or large negative studies tend to be published readily⁷⁷ (suggesting that any missing studies are small and do not demonstrate any difference between allogeneic and control transfusion groups).

A third limitation of this study is the heterogeneity in the postoperative infection analysis. As demonstrated in Table 5, most of the heterogeneity is attributable to two trials^{25,67} from the same research group, and closer examination of the trials reveals several features unique to these two trials that potentially explain the discordant results. First, a substantial minority of the patients did not have cancer and no information was provided on the Dukes' stage or extent of tumour fixation in those who did have colonic cancer, such that it was impossible to determine whether the key prognostic factors were evenly distributed between the two transfusion groups. Second, unlike the other trials, only a minority of patients in the Jensen trials had rectal cancer, an important discrepancy as rectal surgery carries a higher risk of infection and a worse prognosis than other types of colonic surgery^{78,79}.

Third, there appears to have been variability between the Jensen trials and the others included in this analysis in the determination of outcome measures (a crucial point given that none of these studies was double blind). Last, only 1 per cent of control patients in the Jensen trials were transfused with allogeneic blood, whereas 10–35 per cent of control patients in the other trials received crossover blood products. In sum, although the heterogeneity in the results can be explained readily, the presence of heterogeneity of this magnitude decreases the strength of any inferences that can be drawn from the analysis of postoperative infection risk.

Given the lack of evidence for increased risk from allogeneic blood transfusions, it seems appropriate to revisit the role of autologous blood donation programmes. This is particularly important given that almost half of the autologous blood donated before operation in the United States is discarded⁸⁰ and formal economic analyses⁸¹ have questioned the cost-effectiveness of these programmes. Moreover, a previous meta-analysis⁸² and a recent computer modelling study⁸³ demonstrated that, although preoperative donation of autologous blood reduces exposure to allogeneic blood, it increases the likelihood of receiving any blood transfusion nearly threefold. Despite widespread concern over the risk of transmitting infectious diseases, the most common risks with blood transfusion are transfusion reactions, particularly with ABO-incompatible transfusions. As the risk of laboratory, ward or clerical errors leading to transfusion of incompatible blood is the same whether autologous or allogeneic blood is transfused, the increased likelihood of transfusion with autologous predonation implies that this practice may in fact carry more risk than the traditional approach of using allogeneic blood only as needed. Thus, there would need to be strong evidence of potential benefit to justify the widespread implementation of autologous donation programmes.

The authors believe that this meta-analysis provides no evidence for the widely held belief that allogeneic blood carries a significant risk in patients with cancer. While the decision to administer blood must be guided by the clinical situation, it would seem prudent to try to limit perioperative transfusion in all patients, particularly given evidence⁴ that as many as one-third of perioperative blood transfusions in patients with colorectal cancer may be unnecessary.

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Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis

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Background Early detection of infected pancreatic necrosis has a major impact on further management and outcome in acute pancreatitis. The aim of this study was to evaluate the clinical value of ultrasonographically guided fine-needle aspiration cytology (FNAC) in patients with necrotizing pancreatitis over an 8-year period.

Methods From January 1988 to September 1996 193 (mean 2.0 (range 1–9) aspirations per patient) prospectively assessed FNACs guided ultrasonographically were performed in 98 patients with necrotizing pancreatitis proven by contrast-enhanced computed tomography. Aspirates were considered infected if either Gram stain and/or culture revealed micro-organisms.

Results Ultrasonographically guided FNAC correctly diagnosed infection in 29 of 33 patients with infected necrosis a median of 13 days after onset of symptoms. Of 61 patients with sterile necrosis 55 were identified correctly as sterile by FNAC. There were six false-positive and four false-negative aspirates of which nine occurred during the first week of the disease. In four patients who did not undergo operation FNAC revealed Gram-negative organisms; however, in the absence of repeated aspirations, the positive results remained unconfirmed. An overall sensitivity of 88 per cent and a specificity of 90 per cent was obtained. No difference was found in biochemical and clinical parameters indicating systemic inflammatory response syndrome before each FNAC between patients with proven sterile or infected necrosis. All patients tolerated the procedure well and no major complications were observed.

Conclusion Ultrasonographically guided FNAC is a fast and reliable technique for the diagnosis of infected necrosis. As complication rates are very low, the procedure can be repeated at short intervals to improve the diagnostic accuracy. Ultrasonographically guided FNAC is recommended for all patients with necrotizing pancreatitis in whom systemic inflammatory response syndrome persists beyond the first week after onset of symptoms.

Advances in the understanding of the pathophysiology of acute pancreatitis have shown that infection of pancreatic necrosis is the leading complication in the course of this disease. Infection rarely develops in interstitial-oedematous pancreatitis^{1–3}; however, the presence and extent of necrosis significantly increases the incidence of infection up to 80 per cent^{4–9} which is associated with high mortality and morbidity rates^{4,7,10}. Currently, initial treatment of necrotizing pancreatitis should be conservative unless a specific indication for operation arises. In contrast, little disagreement exists about the necessity for surgical intervention in patients with proven infection of pancreatic necrosis^{3,4,7,10}.

As a consequence of the outstanding importance of infection on treatment and outcome in necrotizing pancreatitis an optimum diagnostic tool for its early detection is in demand. Unfortunately, there are neither specific clinical signs^{4,7–9,11,12} nor biochemical tests^{13–17} which allow diagnosis of the presence of infection in necrotizing pancreatitis.

The introduction of contrast-enhanced computed tomography (CT) provided the basis for an objective and accurate morphological stratification of acute pancreatitis^{18–21}. Late entities of pancreatic infections such as pancreatic abscess can be detected by CT. However, extraluminal gas as a pathognomonic feature of infection is found rather infrequently²⁰ and, therefore, early definite diagnosis of infection by CT is still not possible.

In the early 1980s the first reports of fine-needle aspiration cytology (FNAC) guided by CT which allowed direct access to the pancreatic region appeared. On the basis of Gram staining and culturing of the aspirate, reliable diagnosis of infection has become possible. Nowadays, percutaneous guided techniques are well established diagnostic^{11,22–25} and therapeutic^{26–38} methods. The majority of these reports used CT for guidance and focused on complications of acute pancreatitis such as fluid collections^{11,23,24,32,34,38}, pseudocysts^{11,27,29,31,33,35–37}, abscesses^{22,26–28,36} and inflammatory masses¹¹. Surprisingly, only one study has been conducted in the subset of patients with documented necrotizing pancreatitis²⁵ and there are no large-scale studies to validate this technique as accurate in detecting infection in necrotizing pancreatitis as it is in fluid collections, pseudocysts and abscesses.

Experience concerning the diagnostic accuracy and safety of ultrasonographically guided FNAC in a prospective series of patients with necrotizing pancreatitis diagnosed by CT over a period of 8 years is reported.

Patients and methods

Patients

From January 1988 to September 1996 a total of 98 patients with necrotizing pancreatitis underwent FNAC guided ultrasonographically in this department. Patients with morphologically confirmed pancreatic abscesses or postacute pseudocysts were excluded. There were 65 men and 33 women with a median age 52 (range 14–83) years. Some 74 patients (76 per cent) were

referred from other hospitals after a median of 3 (range 1–39) days of conservative treatment; 24 patients (24 per cent) were primary admissions. The overall median time interval between onset of abdominal symptoms and admission to this hospital was 3 (range 0–43) days. No patient had undergone previous necrosectomy or other surgical procedures on the pancreas. The aetiology was alcohol in 51 (52 per cent), gallstones in 26 (27 per cent), endoscopic retrograde cholangiopancreatography in four (4 per cent), and trauma and viral infection in one patient (1 per cent) each. Rare aetiological factors were drugs in four patients (4 per cent) and in 11 (11 per cent) no cause for acute pancreatitis could be found.

Methods

In all patients the presence of necrosis was demonstrated by CT with oral and intravenous contrast medium (CT 9800, General Electric, Chicago, Illinois, USA; CT-Twin flash, Elscint, Haifa, Israel). The intrapancreatic extent of necrosis was graded into less than 30 per cent, 30–50 per cent, and more than 50 per cent of the pancreatic parenchyma. In addition, the serum markers of necrosis, C-reactive protein (CRP)¹³ and lactate dehydrogenase¹⁶, were monitored.

Ultrasonographically guided FNAC was performed if pancreatic infection was suspected by clinical or biochemical signs and symptoms. Clinical signs of infection included persisting systemic inflammatory response syndrome (SIRS) over at least 3 days, biochemical parameters included a persisting raised level of CRP. Some 78 of 193 aspirations in 63 patients were performed within the first 7 days after onset of symptoms and the remaining 115 FNACs in 35 patients during the following weeks.

After written informed consent was obtained, an abdominal ultrasound probe with a frequency of 3.5 MHz (Sonoline SI 450, Siemens, Issaquah, WA, USA; Sonolayer L 77B, Toshiba, Tokyo, Japan) was used to locate the area of necrosis. Following careful skin disinfection, a 22-G sleeve needle (SPINOCAN, Luer Lock, Braun Melsungen, Germany) was advanced under ultrasonographic guidance until the necrotic area was reached and a minimum of 0.1 ml aspirate could be obtained. In general, an aspiration route avoiding bowel or stomach was used in order to minimize the risk of iatrogenic contamination. Thereafter, the aspirate was immediately processed for Gram staining and culture, and interpreted by an experienced microbiologist. An aspirate was considered infected if either Gram stain or culture was positive for micro-organisms. In case of persisting SIRS after confirmation of a sterile aspirate the procedure was repeated up to twice a week. Nearly all aspirations were performed by the same examiner (U.P.).

Initial treatment was conservative in all patients and included maximum intensive care support. Indication for operation was either (1) clear evidence of infection or (2) persisting organ complications or abdominal symptoms despite maximum intensive care measures for 3–5 days in the absence of a positive FNAC result. Thus, 61 patients (62 per cent) underwent necrosectomy and continuous closed lavage of the lesser sac after operation, 35 (36 per cent) were treated without operation, one patient was managed by percutaneous ultrasonographically guided pancreatic abscess drainage and one patient was subjected to late external pseudocyst drainage.

Statistical analysis

All variables are represented as median (range). For comparison of two samples the two-tailed Student's *t* test for interval variables was used. Fisher's exact test was employed for the comparison of proportions. $P < 0.05$ at $\alpha < 0.05$ was considered significant.

Results

A total of 193 aspirations were performed in 98 patients, a mean of 2.0 (range 1–9) aspirations per patient.

Positive aspirates

FNAC revealed positive results in 39 patients by either Gram stain or culture. By comparison with intraoperative bacteriology ($n = 30$), percutaneous drainage ($n = 1$) or subsequent aspirations ($n = 6$), 33 patients were found to have infected necrosis. Intravenous antibiotics were administered in 35 of 39 patients with a positive aspirate. The number of true- and false-positive aspirates as well as the time intervals between onset of pancreatitis and the acquisition of positive results are shown in Table 1. The bacteriological spectrum isolated in the true-positive aspirates is listed in Table 2.

There were six patients with a false-positive result in whom FNAC revealed the following micro-organisms a median of 1 (range 0–5) days before surgery: *Moraxella* and *Candida* in one patient (Gram stain and culture), *Neisseria* and *Streptococcus viridans* in one patient (culture only), *Bacteroides*, *Enterobacter*, *Clostridium perfringens* and *Veillonella* in one patient (Gram stain and culture).

Table 1 Number of aspirations and time interval after onset of symptoms until the true-positive, false-positive and unconfirmed-positive results were obtained

	No. of aspirations	No. of patients
Positive	47	39
True positive	37	29
1 aspirate		17
2 aspirates		6
3 or more aspirates		6
Time after onset of symptoms (days)*	13 (3–44)	
False positive	6	6
1 aspirate		4
2 aspirates		2
Time after onset of symptoms (days)*	4 (1–7)	
Unconfirmed positive	4	4
1 aspirate		1
2 or more aspirates		3
Time after onset of symptoms (days)*	15 (10–22)	

*Values are median (range) time from onset of symptoms to obtaining a positive result

Table 2 Bacteriological findings in 29 patients correctly identified as infected, by ultrasonographically guided fine-needle aspiration (confirmed results only)

	No. of aspirates ($n = 29$)
Monomicrobial	23
Polymicrobial	6
Gram positive	15
Gram negative	14
Fungi only	2
Intestinal organisms	21
Non-intestinal organisms	8
Organisms*	
<i>Enterococcus</i>	7
<i>Escherichia coli</i>	7
<i>Klebsiella</i>	7
<i>Staphylococcus aureus</i>	5
<i>Citrobacter</i>	1
<i>Pseudomonas</i>	1
<i>Enterobacter</i>	1
<i>Candida</i>	3

*Two patients had negative cultures

Table 3 Negative aspirations and number of procedures per patient

	No of aspirations	No. of patients
Negative	112	59
True negative	108	55
1 aspirate		28
2 aspirates		12
3 or more aspirates		15
False negative	4	4
1 aspirate		4

and *Staphylococcus aureus* in three patients (two by Gram stain and culture, one by culture only).

Two patients with proven infected necrosis were managed without an operation. One, a 79-year-old patient with high co-morbidity, was in a severe clinical condition that did not allow surgery and died from fulminant septic multiorgan failure as a consequence of infected necrosis.

There were four patients with a non-confirmed positive aspirate. As all of them were managed conservatively, intraoperative or interventional bacteriology was not available and another aspiration was not performed. Aspirates revealed *Escherichia coli* (in one patient by Gram stain and culture; in one patient by culture only), *Proteus* (Gram stain and culture), and Gram-negative bacteria (Gram stain only). Although persisting SIRS was the indication for FNAC, the clinical condition in terms of organ dysfunction was already improving in all four patients at time of the positive FNAC result. Therefore, conservative therapy was continued. One patient died several weeks later from acute cardiac failure not related directly to necrotizing pancreatitis; the remaining three left hospital in good clinical condition.

Based on patients with confirmed positive FNAC results, a diagnostic sensitivity of 88 per cent (29 patients with a positive FNAC of 33 patients with proven infection) and a positive predictive value of 83 per cent (29 patients with a true-positive FNAC of 35 patients with a confirmed positive FNAC).

Negative aspirates

A total of 59 patients were found to have sterile necrosis by one or more ultrasonographically guided FNAC. The negative aspirates were confirmed in 55 of 59 patients by intraoperative findings ($n=25$), by repeated aspirations and complete resolution of symptoms ($n=17$), or by complete resolution of symptoms alone ($n=13$). Intravenous antibiotics were administered in 49 of 59 patients with negative FNAC results. In Table 3 the number of aspirations in the patient group with true- and false-negative aspirates are shown.

In four patients with intraoperatively proven infected necrosis FNAC was false negative a median of 3 (range 1–17) days before surgery. Despite the negative aspirate, intraoperative smears revealed infection with *E. coli* and *Aeromonas hydrophila*, *E. coli* and *Enterococcus*, *Klebsiella*, and *Enterococcus* and *Bacteroides ovatus*.

The specificity of the procedure was 90 per cent (55 patients with a negative FNAC of 61 patients with confirmed sterile necrosis) with a negative predictive value of 93 per cent (55 patients with a true-negative FNAC of 59 patients with a negative FNAC). The overall results of this ultrasonographically guided approach to FNAC are summarized in Table 4.

Table 4 Overall results of ultrasonographically guided fine-needle aspiration in 94 patients with necrotizing pancreatitis

	Confirmed*	
	Positive ($n=33$)	Negative ($n=61$)
FNAC		
Positive ($n=35$)†	29	6
Negative ($n=59$)	4	55
Sensitivity (%)	88	
Specificity (%)		90

*Positive results were confirmed by intraoperative or interventional therapy and repeated aspiration, and negative results by intraoperative findings, repeated aspiration, and clinical and morphological recovery. †Four non-confirmed positive aspirations in four conservatively treated patients were excluded FNAC, fine-needle aspiration cytology

Table 5 Results of contrast-enhanced computed tomography in patients with true sterile and infected necrosis diagnosed by fine-needle aspiration

	FNAC positive	FNAC negative	P
Contrast-enhanced CT	29	55	
Intrapancreatic necrosis (%)	28	50	
<30	4	24	0.003
30–50	10	15	n.s.
>50	14	11	0.01
Extrapancreatic necrosis only	0	3	
Cystic mass*	1	2	

*Cystic mass confirmed as extrapancreatic necrosis at operation. FNAC, fine-needle aspiration cytology; CT, computed tomography; n.s., not significant (Fisher's exact test)

The timing of FNAC with respect to the onset of symptoms had an impact on the diagnostic accuracy. Three of four false-negative aspirates and all six false-positive results were observed within the first week after the onset of symptoms. Only one false-negative and no false-positive aspirate was observed if FNAC was performed during the second week of necrotizing pancreatitis or later.

No serious complications were experienced. There was no pancreatic infection which could be clearly ascribed to this procedure, even in 17 patients who underwent repeated aspirations after a first sterile culture. In general, the procedure was well tolerated.

Clinical and morphological parameters

To further assess the importance of ultrasonographically guided FNAC in discriminating sterile from infected necrosis, CRP level, leucocyte count, body temperature and pulse rate were monitored over 72 h before each confirmed positive ($n=37$) and negative ($n=108$) aspiration. Although levels of all of the variables were above normal, there were no significant differences between patients with sterile and infected necrosis.

The extent of intrapancreatic necrosis assessed by contrast-enhanced CT was significantly greater in patients with infected necrosis confirmed by FNAC than in patients with sterile necrosis (Table 5). The clinical severity of necrotizing pancreatitis did not differ between patients with sterile necrosis (median Ranson score 5

(range 0–10); median Acute Physiology And Chronic Health Evaluation (APACHE) II score 12 (range 2–28) and those with infected necrotizing pancreatitis (median Ranson score 5 (range 2–9); median APACHE II score 12 (range 4–29)) proved by FNAC.

Discussion

Percutaneous interventional techniques have gained considerable importance in the diagnosis and management of patients with acute pancreatitis. A number of studies have validated this approach as safe and reliable with respect to its diagnostic^{11,22–25} and therapeutic^{26–38} role. In a number of recent studies, guided FNAC provided the bacteriological stratification for the evaluation of different treatment strategies^{7,8,39,40}. Surprisingly, there are no large-scale studies to validate this technique as accurate in detecting infected necrosis as it is in fluid collections, pseudocysts and abscesses, although it is well known that these entities of acute pancreatitis are characterized by a different morphology which may influence the diagnostic accuracy of the technique.

The present study reports an experience with FNAC using an ultrasonographically guided approach in 98 patients with necrotizing pancreatitis documented by CT. A diagnostic sensitivity of 88 per cent, specificity of 90 per cent, and accuracy of 89 per cent were obtained. Compared with previous studies, which uniformly obtained a sensitivity and specificity of more than 90 per cent (Table 6)^{11,22–25}, these results are slightly less favourable.

The most important factor for the diagnostic accuracy of guided FNAC in this series seems to be the time after onset of symptoms at which the procedure is performed. All six false-positive and three of four false-negative aspirates were observed when FNAC was performed within the first week of the disease. As the majority of patients with necrotizing pancreatitis develop infection around the third week of the disease, there is no doubt that FNAC is indicated during this time. In contrast to previous reports^{11,25} the present results demonstrate for the first time that FNAC may be problematic, if performed early in the course of necrotizing pancreatitis. On the other hand, about 20 per cent of patients develop infection within the first week of the disease^{4,11,39}, in this series seven of 33 patients, so it can hardly be argued that there is absolutely no indication for FNAC during the earlier stages of necrotizing pancreatitis.

The bacteriological spectrum of the false-positive aspirates was different from that of the true-positive

aspirations obtained during the first week after onset of symptoms. In the true-positive samples predominantly Gram-negative bacteria of intestinal origin were found; in the false-positive aspirates Gram-positive bacteria of non-intestinal origin were present. In both groups the patients received the same prophylactic antibiotic regimen and had a similar extent of intrapancreatic necrosis. The presence of Gram-positive bacteria in the false-positive aspirates therefore strongly suggests exogenous contamination and thus a complication of FNAC, but it remains unclear why all of them occurred within the first week of the disease. After operation, all six patients with the false-positive FNAC recovered and were discharged in good clinical condition. However, in these patients another FNAC could have contributed to the correct diagnosis which might have changed the subsequent treatment. As a consequence, positive FNAC results in the early course of acute pancreatitis should be considered with caution and should be confirmed by another aspiration. Whenever possible, FNAC should be postponed to the second week or later.

Methodological factors may have played a role in the false-negative results. The majority of reports advocate contrast-enhanced CT as the guiding device of choice for FNAC^{11,22–24}, as it is currently an imaging procedure which provides the most objective and accurate information about morphological alterations in acute pancreatitis. All patients in the present series underwent CT before ultrasonographically guided aspiration for localization of the areas and extent of necrosis. On the basis of CT findings exact targeting of the needle was generally no problem. However, it has to be emphasized that ultrasonographic expertise is the critical factor for accurate localization of the area to be aspirated, especially in the presence of obesity or abdominal meteorism. On the other hand, there are a number of advantages of ultrasonographic guidance: this technique is performed at the bedside without need for transportation of the often severely ill patient, the cost is less and there is no radiation exposure. Thus, repeated aspirations are faster and easier to perform when guided by ultrasonography than by CT which explains the higher aspiration frequency in this series. Another critical factor for the false-negative results may be time needed for the transportation of the aspirates to the department of microbiology for Gram staining, culturing and interpretation. Some bacterial strains could have been damaged with the consequence of a false-negative result. Immediate processing and analysis of the aspirate is ideal. In addition, a possible impact of the usually solid nature of infected necrosis compared with the fluid content of pseudocysts or abscesses has to

Table 6 Diagnostic guided fine-needle aspiration in acute pancreatitis: review of the literature

Reference	Year	Guide	n	Sensitivity (%)	Specificity (%)	
Barkin <i>et al.</i> ²²	1982	CT/US	13	90	100	Abscess
Hiatt <i>et al.</i> ²³	1987	CT/US	18	94	n.r.	Abscess
Gerzof <i>et al.</i> ¹¹	1987	CT	60	100	98	Pseudocyst
						Pseudocyst
						Extrapaneatic fluid collection
Banks <i>et al.</i> ²⁵	1990	CT	15	100	100	Phlegmon
Stiles <i>et al.</i> ²⁴	1990	CT	35	92	96	Necrotizing pancreatitis
						Pancreatic fluid collection

CT, computed tomography; US, ultrasonography; n.r., not reported

be taken into account. However, a study in seven patients has shown that the pancreatic exudate, which is easier to aspirate than solid necrosis, yields the same bacteria as found in the infected tissue²⁵, but this has never been proved in larger patient series.

Four positive aspirates in four patients who were treated conservatively remain speculative and were therefore not included in the sensitivity and specificity calculation. At the time of the positive FNAC result the clinical condition of these patients had already improved so that the decision was made to continue conservative treatment. In the absence of a subsequent aspirate it is difficult to judge what the positive aspirates really represented. They could in fact be another four false-positive results; however, both the Gram-negative bacteriological spectrum and the time of occurrence do not speak in favour of iatrogenic infection. A possible role for conservative treatment in selected patients with infected necrosis has been reported recently in a small series⁴¹. Thus, it has to be considered that infection or at least contamination had been present in these patients.

From various reports guided FNAC is known to be a safe technique with a low complication rate. Very few serious complications such as bleeding, aggravation of acute pancreatitis or death are reported in the literature⁴²⁻⁴⁵ and were not observed in this series. Although there were six false-positive aspirates which should be considered as complications, no patient developed infected necrosis which clearly could be attributed to the procedure itself. The authors are able to confirm that even repeated aspirations, if performed in experienced hands, do not carry an increased risk of iatrogenic infection or complications. In addition, no clinical or routine biochemical parameter is able to differentiate reliably between sterile and infected necrosis, in accordance with other authors^{9,11,25}, which underscores the importance of this procedure.

In summary, guided FNAC is a reliable technique to differentiate sterile from infected necrosis in acute pancreatitis. Ultrasonographic guidance renders the procedure fast to perform, well tolerated by the patient and cost effective. As complication rates are very low, ultrasonographically guided FNAC can be repeated at short intervals to improve diagnostic accuracy. This procedure is recommended for use in every patient with necrotizing pancreatitis in whom SIRS persists beyond the first week after onset of symptoms. In this respect, the importance of exact targeting of the aspiration needle, maintenance of sterile conditions during aspiration and rapid processing of the specimen, as well as an immediate work up for bacteriology, has to be underscored.

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Hepatic resection with cryotherapy to involved or inadequate resection margin (edge freeze) for metastases from colorectal cancer

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Background In patients undergoing liver resection for colorectal liver metastases, a resection edge either involved by tumour or with the tumour extending to within 1 cm is associated with a high risk of liver recurrence and survival is reduced markedly.

Methods Twenty-six patients underwent cryotherapy of the resection edge following liver resection for metastases from colorectal carcinoma with an involved or inadequate (less than 1 cm) resection margin.

Results At a median follow-up of 23 (range 1–47) months four patients were alive and disease free, and 21 had developed recurrence, of whom 13 had died. One patient died following surgery. Sixteen patients developed recurrences involving the liver, only five of which were at the resection margin.

Conclusion Cryotherapy to involved or inadequate resection margins improves local disease control considerably. The use of resection edge cryotherapy might allow a greater proportion of patients with liver metastases to be usefully treated and help to avoid high-risk resections.

Liver resection is the only well established treatment for patients with liver metastases from colorectal cancer, with 5-year survival rates of up to 50 per cent^{1–3}. Following liver resection the number of metastases treated and adequacy of the resection margin are the most important prognostic factors^{4–6}. In patients with a resection edge either involved by tumour or with the tumour extending to within 1 cm, there is a high risk of liver recurrence and survival is reduced markedly⁴.

Several reports of cryotherapy for irresectable primary or secondary liver tumours have been published^{7–12}. This paper reports the results of cryotherapy of the resection edge following liver resection for metastases from colorectal carcinoma with an involved or inadequate (less than 1 cm) resection margin.

Patients and methods

A total of 32 patients were treated with combined liver resection and edge cryotherapy by one surgeon during the period from February 1992 to August 1995. Of these, 26 patients had metastases from colorectal cancer and are the subject of this report. There were 12 men and 14 women of median age 59 (range 30–81) years. Two patients had previously undergone liver resection. All patients underwent preoperative screening (pulmonary computed tomography (CT), CT portography, bone scanning) to exclude extrahepatic metastases and to assess the liver disease.

In all patients laparotomy was performed initially through a bilateral subcostal incision to exclude extrahepatic disease. Enlarged portal lymph nodes were sent for histological examination by frozen section. The liver was then assessed with intraoperative ultrasonography, and resection was carried out under portal inflow occlusion using an ultrasonic dissector. The type of hepatic resection performed is shown in *Table 1*. After removal of the specimen, the adequacy of the resection margin was assessed by the surgeon and, if less than 1 cm, cryotherapy was applied to the margin.

Cryotherapy was delivered using the Cryotech LCS 3000 liquid nitrogen-based system (Spemby, Andover, UK) as described previously¹³. The reasons for performing cryotherapy to the resection edge, instead of more extended resection, are shown in *Table 2*. Cryotherapy was administered to a depth of 1 cm using plate or spike probes. Two patients underwent synchronous colonic resection to remove the primary tumour. Adjuvant hepatic artery chemotherapy was used in nine patients (*Table 3*).

Follow-up is ongoing with clinical examination and determination of carcinoembryonic antigen (CEA) levels every

Table 1 Type of hepatic resection

	No. of patients
Extended right hemihepatectomy	5
Right hemihepatectomy*	7
Left hemihepatectomy†	6
Left lateral segmentectomy‡	3
Segmental resection	5

*Plus additional wedge resection of segment 3 in two patients;

†plus additional resection of parts of segment 5 in two patients;

‡plus contralobe cryotherapy for an additional metastasis in one patient

Table 2 Reasons for performing edge cryotherapy

	No. of patients
Proximity of contralateral hepatic veins or portal sheath	6
Avoidance of extended right hemihepatectomy	5
Avoidance of extended left hemihepatectomy	5
Inadequate liver tissue reserve	8
Repeated liver resection	1
Patient unfit for major resection	1

Table 3 Comparison of patients receiving hepatic artery chemotherapy with those who did not

	HAC	No HAC
No. of patients	9	17
Median (range) no. of metastases	2 (1-4)	1 (1-5)
Median (range) length of follow-up (months)	27 (15-35)	22 (1-47)
No. of patients with liver recurrence	5	11
Median(s.e.) disease-free survival (months)	11(1)	14(8)
Median(s.e.) liver disease-free survival (months)	23(6)	15(5)

HAC, hepatic artery chemotherapy

3 months. In 16 patients with raised serum CEA levels before operation that returned to normal following liver resection, an eventual CEA relapse was followed by abdominal and pulmonary CT to locate recurrent tumour. In CEA non-secretors, abdominal CT and chest radiography were performed every 3 months. In patients who died from progressive disease, autopsy was not performed routinely. The survival time and recurrence-free intervals were estimated by means of Kaplan-Meier life-table analysis

Results

The median number of metastases treated in this group of patients was 1 (range 1-5) and the median diameter of the largest lesion was 5 (range 2-20) cm. Median freezing time was 7 (range 3-15) min. Median postoperative stay was 8 (range 5-27) days. Mean intraoperative blood replacement was 1.92 units of packed cells, with 13 patients receiving no blood. Five patients developed bile collections requiring percutaneous drainage and one patient underwent laparotomy for postoperative bleeding. One patient died 23 days after surgery from acute pancreatitis complicated by an abscess.

Histological examination showed the resection margin to be involved in 16 patients and to be close (less than 1 cm) in ten.

The median follow-up period was 23 (range 1-47) months, including the patient who died after operation. Of the 25 patients who left hospital, four are currently alive and disease free 22, 22, 28 and 33 months after liver resection. Twenty-one patients developed recurrence; 13 of them died 5-39 (median 18) months after liver resection and eight are alive with recurrence at 19-47 (median 29.5) months. In 21 patients with recurrent disease, the liver was involved in the first manifestation of recurrence in 13 patients: liver at the resection edge which was treated by cryotherapy (four), liver at the resection edge and lung (one), liver only far from resection edge

(five), liver only far from resection edge and lung (three). In eight patients the first site of recurrence was extrahepatic: lung (four), lung and bone (one), bone (one), local recurrence of the primary tumour (one), recurrence in the laparotomy scar (one). Five of these 21 patients had repeated resections of the recurrence with curative intent: cryotherapy for edge recurrence (one) or non-edge recurrence (two), removal of lung metastases (one), resection of recurrence in laparotomy scar (one).

At the latest follow-up or at time of death the liver was involved in 16 of the 21 patients with recurrent tumour, with involvement of the resection edge in five patients. The estimated recurrence-free intervals for the resection edge, the liver and overall for patients with involved and close margins are shown in *Table 4*.

The median(s.e.) overall estimated survival time for all 26 patients treated was 29(7) months, with 39(5) and 24(5) months for those with close ($n=10$) and involved ($n=16$) margins respectively ($P=0.44$, log rank test).

Discussion

Hepatic cryotherapy appears to be a useful technique for treating irresectable hepatic metastases. Its use as an adjunct to resection has not previously been reported independently. Cady *et al.*⁴ reported a series of patients undergoing hepatic resection including ten who had combined resection and cryotherapy, although this small group was not analysed in detail. Another group reported on 12 patients who received edge cryotherapy for close (seven) or involved (five) margins after liver resection for colorectal liver metastases¹⁴. Median disease-free survival was 19.5 months and mean overall survival was 31 months. No details on the site of recurrence were given for this group of patients.

Adequate tumour clearance is the major risk factor for local recurrence after liver resection^{15,16}. The probability of being disease free at 5 years falls from 50 to 18 per cent for patients with uninvolved resection margins with clearance of greater and less than 1 cm respectively⁴. When the resection margin is involved, liver recurrence is inevitable⁴, occurring in 80 per cent of patients within 12 months of resection. In the present series, 12 of 16 patients with involved resection margins developed liver recurrence, with a median(s.e.) liver disease-free survival of 15(4) months; only four of the 12 developed recurrence at the resection edge, with a mean(s.e.) resection edge disease-free survival of 29(3) months. At 1 year post-resection, however, only six of the 16 patients had liver recurrence, compared with 80 per cent in the series of Cady *et al.*⁴, and recurrence occurred at the resection edge in only one patient.

Table 4 Site of and time to recurrence in 25 patients (hospital mortality excluded)

	Involved margin ($n=16$)		Close margin ($n=9$)		Total ($n=25$)	
	n	Estimated disease-free survival (months)	n	Estimated disease-free survival (months)	n	Estimated disease-free survival (months)
Total recurrence	15	10(3)*	6	16(6)*	21	12(3)*
Liver recurrence	12	15(4)*	4	22(4)†	16	18(4)*
Resection edge recurrence	4	29(3)†	1	36(3)†	5	33(2)†

*Median(s.e.) and †mean(s.e.) values

In the present patients with close margins four developed recurrent liver disease with a mean(s.e.) liver disease-free survival of 22(4) months. Only one of these recurrences was located at the resection edge, with a mean(s.e.) resection edge disease-free survival of 36(3) months. Cryotherapy clearly failed in five patients who developed recurrence at the resection margin, but this appears to be a considerably lower rate than would have been expected without edge freeze. It seems unlikely that the hepatic artery chemotherapy used in some of the patients affected these results: time until recurrence did not differ significantly between the two groups (Table 3).

Bile leaks occurred in five of the 26 patients, a rate that is comparable to some series of liver resection¹⁷. As bile ducts are particularly susceptible to cryoinjury¹⁸, edge cryotherapy may increase the risk of bile collections following liver resection. The use of drains in this situation is mandatory. The single postoperative death in the present series was not associated with cryotherapy.

These data suggest that cryotherapy to involved or inadequate resection margins improves local disease control considerably. The use of resection edge cryotherapy may allow a greater proportion of patients with liver metastases to be treated usefully with the avoidance of high-risk resection due to inadequate residual liver volume or particular resection types, such as extended left hemihepatectomy.

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Correlation between blood loss and inferior vena caval pressure during liver resection

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Background Blood loss and transfusion requirement are major determinants of mortality and morbidity following liver resection. This study was prompted by the observation that blood loss was excessive when the inferior vena cava (IVC) was distended, and determined whether a correlation exists between blood loss and pressure within the IVC during liver resection.

Methods A 6-month prospective study was conducted on 20 consecutive patients undergoing liver resection in which two variables were measured, the pressure within the retrohepatic part of the IVC and blood loss during resection.

Results It was observed that when the caval pressure was less than 6 mmHg the operating field was almost bloodless (mean blood loss 363 (range 305–465) ml). When the caval pressure was between 6 and 12 mmHg the liver became congested and bleeding from the liver surface became significantly greater (1259 (range 415–1789) ml). When caval pressure was greater than 13 mmHg bleeding became excessive (2703 (range 2360–3450) ml). Correlation between blood loss and caval pressure was strong (Pearson correlation coefficient 0.93, $P < 0.001$).

Conclusion This study suggests that one of the keys to decreasing blood loss and transfusion requirement during liver resection is to lower pressure within the IVC.

Numerous studies have been published in the past 10 years suggesting predictors of outcome following liver resection^{1,2}. More recent publications suggest that blood loss and transfusion requirement are extremely important determinants of morbidity and mortality following liver resection^{3,4}. This is because of the risk of coagulopathy and the immunosuppressive effects of transfused blood. Additionally, blood transfusion may increase transmission of pathogens, unwanted reactions and cost.

Historically, blood loss during liver resection has been extensive. Sophisticated instrumentation (ultrasonic aspirator, jet cutter and intraoperative ultrasonography) and various operative techniques (Pringle's manoeuvre and total vascular occlusion), together with the establishment of the segmental nature of liver anatomy by Couinaud, have allowed resection to be performed safely with decreased intraoperative blood loss^{5–14}.

This study was prompted by the observation that, when the inferior vena cava (IVC) was distended, blood loss during resection was excessive, but when the IVC was lax blood loss was minimal. This relationship is suspected by liver surgeons and it is accepted on the basis of anecdote and experience. Objective investigation of this relationship has not been reported previously, so its form and parameters remain undefined. The aim of this prospective study was to establish by direct intraoperative measurement the relationship between pressure within the IVC and blood loss during liver resection.

excluded, giving a total of 20 evaluable patients. All resections were of a similar magnitude, either hemihepatectomy or extended hemihepatectomy. Segmental resections and non-anatomical resections were excluded from the study.

Measurement of caval pressure

A 2-mm umbilical catheter was inserted into the IVC, 2 cm superior to the junction with the renal veins, just before liver resection, and advanced so as to lie in the retrohepatic part of the IVC, in close proximity to the hepatic veins. It was secured by a purse-string suture. After calibration, the catheter was connected to a pressure transducer with a digital display. Pressure changes were recorded twice before resection and then at 15-min intervals related to the Pringle manoeuvre and during the 10-min intervals when the hepatic inflow was restarted.

A value for the mean caval pressure was calculated for each liver resection from the results recorded in each cycle

Measurement of blood loss

Blood loss was measured at alternate 15- and 10-min cycles, and in each cycle was the sum of the following three variables: volume of blood in the return bottle of the ultrasonic aspirator, volume of blood in the assistant's suction bottle and volume of blood on the wet swabs. Total blood loss during liver resection was the sum of the volumes of blood loss for each cycle.

Measurement of blood loss commenced at the start of resection of the liver parenchyma and finished when the resected specimen was removed. It did not include measurement during initial entry into the peritoneal cavity or mobilization of the liver.

Statistical analysis

Parametric Pearson correlation coefficients between two variables were computed using a statistics package (SPSS, Chicago, Illinois, USA) (blood loss with caval pressure, blood loss with number of measurements). Number of measurements was used as an indicator of duration of surgery.

Non-parametric Spearman correlation coefficients were also computed and were of similar magnitude.

Patients and methods

Some 24 consecutive patients scheduled to undergo major liver resection were studied. Four patients were found to have inoperable disease following a trial dissection and were thus

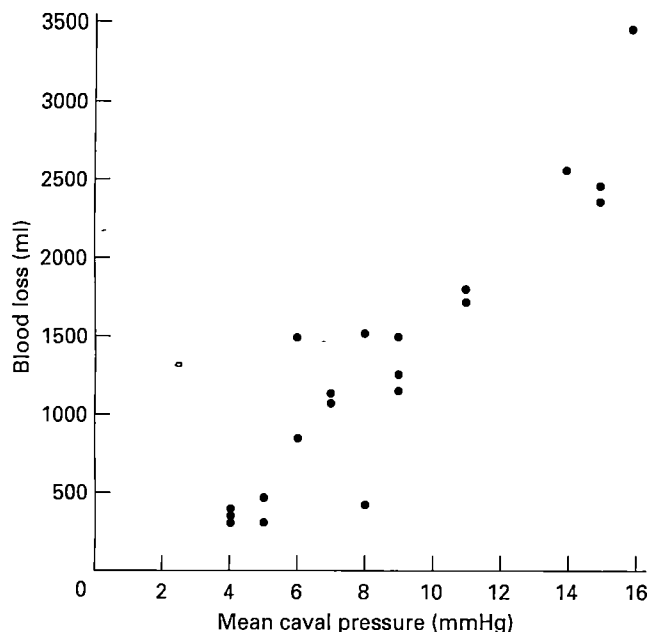


Fig. 1 Correlation between blood loss and inferior vena caval pressure during liver resection

Results

The correlation between mean pressure within the IVC and total blood loss during liver resection was strong (Pearson correlation coefficient 0.93, $P < 0.001$) (Fig. 1). When caval pressure was 5 mmHg or less, blood loss was always less than 500 ml ($n = 5$). However, when mean caval pressure rose to more than 14 mmHg, blood loss was excessive at over 2000 ml in each case ($n = 4$).

Blood loss was not related to the length of operation, as indicated by the number of measurements. The partial correlation coefficient between caval pressure and blood loss, after controlling for the number of measurements, was 0.92 ($P < 0.001$).

No complication was observed in any patient as a result of cannulation of the IVC or resulting from a low caval pressure. There were no deaths in this study, but a difference in morbidity was noted between patients with a high caval pressure (7 mmHg or more) and those with a low caval pressure (less than 7 mmHg). There were four postoperative complications in the former group and none in the latter group. All four complications prolonged hospital stay.

Discussion

Mortality and morbidity rates following liver resection are known to be influenced significantly by blood loss and blood transfusion¹⁵⁻²⁰. This is attributed to increased risks of coagulopathy, acute respiratory distress syndrome and multiorgan failure. In the long term, there is laboratory and clinical evidence to suggest that the immunosuppressive nature of blood transfusion may lead to earlier tumour recurrence. Blood transfusion has long been known to afford improved kidney transplant survival²¹. Transfusions increase suppressor T cell activity²², inhibit natural killer cell activity²³, increase levels of α_2 -macroglobulin (a protease inhibitor that causes non-specific lymphocyte suppression)²⁴ and increase levels of

prostaglandin E_2 (which activates suppressor T cells and inhibits interleukin 2 production)²⁵. Furthermore, the mitogenic activity of platelet-derived growth factors increases during storage of blood and may stimulate tumour growth following transfusion²⁶. Perioperative transfusion may, therefore, stimulate tumour growth directly or by an immunosuppressive effect, thereby having an adverse effect on patient survival.

Blood loss during liver resection has always been a major problem because of the inherent vascularity of the organ. Recent innovations in instrumentation and techniques, together with an increased understanding of liver anatomy, have resulted in a decrease in blood loss during this form of surgery. In the present study, utilizing fluid restriction, one-third of the patients required no blood transfusion. However, in a proportion of cases blood loss was still considerable. Tumour size and surgical expertise are important contributing factors. Larger, posteriorly positioned tumours are known to incur greater blood loss at resection¹³. However, overinfusion of fluids and some degree of right-sided heart failure may also be contributory.

The results from this study clearly demonstrate a strong correlation between blood loss and pressure within the IVC. This effect may be attributable to backbleeding via the hepatic veins. Consequently, the higher the IVC pressure, the greater the venous engorgement of the liver, leading to increased blood loss during resection.

The observations show that pressure within the IVC is extremely important when considering factors influencing operative blood loss. Surgical and anaesthetic teams should be aware that a high caval pressure, from over-enthusiastic fluid infusion or a degree of congestive cardiac failure, can be deleterious and attempts should be made to reduce it as long as this is compatible with haemodynamic stability. In this series not all patients could tolerate a lower caval pressure, and venous return to the heart and cardiac output may fall. If the caval pressure is seen to be high, then a combination of judicious fluid restriction, and use of diuretics and the Trendelenburg position are standard procedures, both to reduce caval pressure and to minimize the consequences of air embolism in the rare event that this should occur. It is important to note, however, that this regimen is not appropriate if total vascular exclusion is employed, when a much higher caval pressure is desirable before clamping²⁷.

Investigation into the effects of venovenous bypass are presently under way in an attempt to reduce bleeding and transfusion requirements in difficult cases where blood loss is excessive despite the use of these standard procedures.

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Bile duct injury during laparoscopic cholecystectomy without operative cholangiography

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Background The role of operative cholangiography in the prevention of bile duct injuries is controversial. A prospective audit of biliary injury is presented.

Methods Laparoscopic cholecystectomy without operative cholangiography was undertaken in a consecutive series of 1200 patients. All biliary injuries were recorded.

Results Meticulous dissection proved to be a reliable safeguard against injury to the right hepatic, common hepatic and common bile ducts. However, four accessory ducts were sacrificed and localized injury to the common hepatic or common bile duct occurred in three patients. These injuries would not have been prevented by operative cholangiography.

Conclusion Operative cholangiography is not a prerequisite for the safe performance of laparoscopic cholecystectomy and cannot be relied upon to prevent all biliary injuries.

Injury to the biliary tree is a well documented complication of laparoscopic cholecystectomy. This paper reports the bile duct injuries that occurred in a consecutive series of 1200 patients undergoing laparoscopic cholecystectomy performed without intraoperative cholangiography. Some injuries to accessory ducts proved impossible to avoid. The inability to detect the ducts by operative cholangiography is demonstrated.

Patients and methods

All patients who underwent laparoscopic cholecystectomy in a consecutive series between 1990 and 1996 were included in the study. A standard four-port technique was used. Operative cholangiography was not performed except in one patient at the beginning of the series. Selective preoperative endoscopic retrograde cholangiopancreatography (ERCP) was undertaken when ductal stones were suspected. The dissection technique used to avoid injury to the major bile ducts began by stripping the peritoneal covering in the region of Hartmann's pouch medially. Fat and areolar tissue were subsequently dissected in the same direction to expose the cystic duct and cystic artery (Fig. 1). When the cystic artery could be identified clearly it was

divided before division of the cystic duct thereby helping to 'open up' Calot's triangle. The junction between the cystic duct and the common bile duct (CBD) was not sought to avoid risk of injury to the CBD.

Using blunt dissection, Hartmann's pouch was elevated from the liver to create a space between the cystic duct and Hartmann's pouch on the one hand and the liver on the other. Provided that no structure was seen to cross this space and the cystic duct could be seen to enter Hartmann's pouch, the cystic duct was safely clipped and divided. The gallbladder was then dissected from the liver using diathermy and delivered via the epigastric port. All injuries to the extrahepatic duct system were audited and patients were followed for 2–5 years. In each case the possibility that an intraoperative cholangiogram would have enabled the surgeon to avoid the injury was assessed.

Results

There were no major injuries to major extrahepatic ducts (transection or stricture). However, there were injuries to accessory ducts in four patients and in three patients the CBD or common hepatic duct (CHD) was injured (Table 1).

Division of accessory right hepatic duct

The position of the accessory ducts and the mechanism of injury is shown in Fig. 2. Historical details are shown in

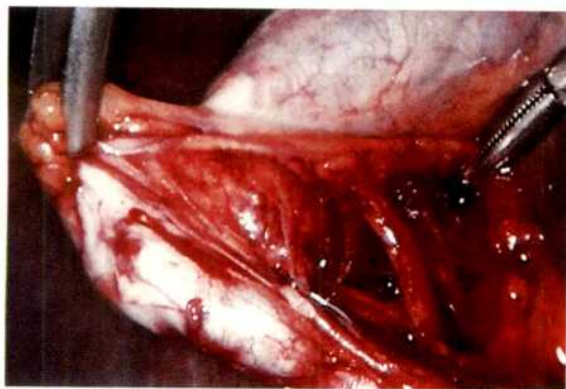


Fig. 1 Dissection of Calot's triangle before cystic duct transection. When feasible, the cystic artery (seen to the right of the cystic duct) is divided before the cystic duct

Table 1 Biliary injuries occurring in 1200 laparoscopic cholecystectomies without operative cholangiography

Duct injury	n	Action	Outcome
Division of accessory right hepatic duct	2	Laparotomy; ligated	Uneventful*
Division of cholecystohepatic duct	2	Clipped	Uneventful
CHD tear	2	Laparotomy; T tube	Uneventful
'Clip-induced' necrosis at CBD–cystic duct junction	1	Laparotomy; T tube	Uneventful

*One biliary fistula closed spontaneously. CHD, common hepatic duct

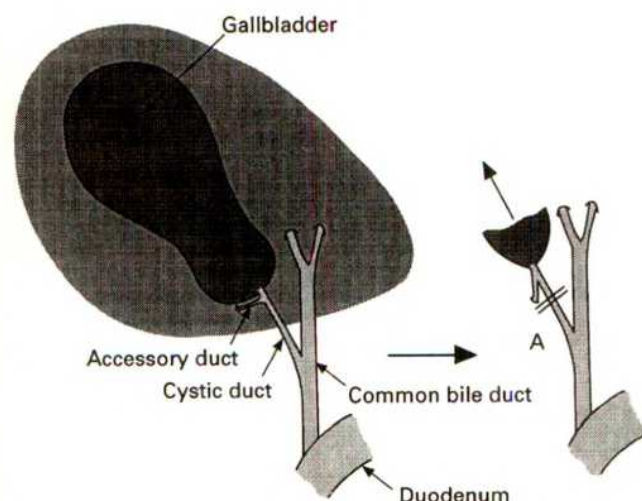


Fig. 2 Diagrammatic representation of accessory right hepatic duct and the point of division (A) of the cystic duct in two patients

Table 2. In neither patient was there any indication on routine preoperative assessment that there was an accessory duct. Preoperative ERCP in one of the patients was normal and did not show any communication between the main duct system and the accessory duct. In both patients laparoscopic cholecystectomy proceeded uneventfully until the point where the cystic duct was divided. In both patients the CBD and CHD had been visible and were intact. In neither patient was the accessory duct seen although Hartmann's pouch was separated from the liver. After division of the cystic duct at point A (Fig. 2) it became clear that a small duct progressed cranially into the liver having originated close to the junction of the cystic duct and the gallbladder. In both cases a laparotomy was performed and a cholangiogram of the main extrahepatic biliary tree showed no evidence of communication between the accessory (divided) duct and the main extrahepatic biliary system. The proximal end of the divided duct was ligated. In one patient there was a completely uneventful recovery and he remains well 5 years later. In the other patient (Table 2) a biliary fistula

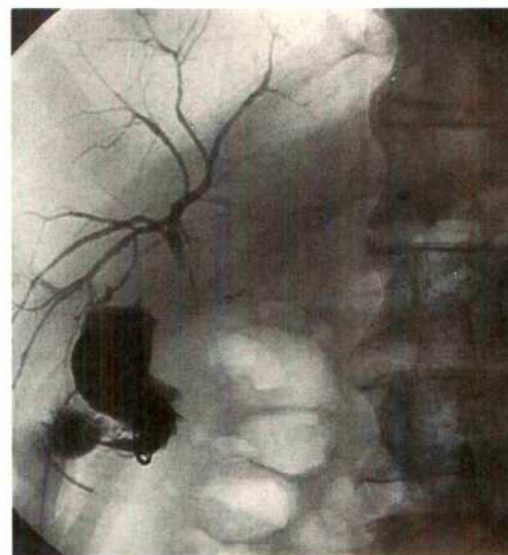


Fig. 3 Percutaneous 'fistulogram' reveals a divided right accessory duct. Spontaneous closure of the fistula occurred 18 days after cholecystectomy

became apparent on the first day after operation due to slippage of the ligature on the divided accessory duct. ERCP was performed, which showed no evidence of any communication between the main duct system and the accessory duct. The biliary leak was not demonstrated. The biliary fistula drained 200 ml per 24 h and a percutaneous fistulogram (Fig. 3) outlined the divided accessory right hepatic duct. The biliary fistula was managed conservatively and on the 18th day after operation it closed spontaneously. The patient has been well and was last seen 3 years after the operation. In both of these patients an operative cholangiogram performed via the cystic duct would not have detected the accessory duct and would, therefore, not have prevented the injury.

Division of cholecystohepatic duct

There were two patients in whom a small biliary channel was noted to open into the gallbladder itself (Fig. 4). One entered the body of the gallbladder and the other entered Hartmann's pouch quite close to the junction with the cystic duct. These accessory ducts were noticed during dissection of the gallbladder and were clipped and ligated. Neither patient suffered any ill effects.

Common hepatic duct tears

In two patients in whom the gallbladder was adherent to the CHD, dissection of Hartmann's pouch away from the duct proved difficult. The CHD was seen clearly but was opened inadvertently during dissection of the gallbladder away from it. In both patients the placement of a T tube at laparotomy was followed by an uneventful recovery (Fig. 5). In these two patients operative cholangiography would have been difficult to perform and would not have prevented the tear in the CHD which occurred during deliberate dissection of Hartmann's pouch away from that duct.

Table 2 Details of two men in whom an accessory right hepatic duct was transected inadvertently

	Patient 1	Patient 2
Age (years)	70	68
Preoperative investigations	Ultrasonography LFT (raised serum alkaline phosphatase)	Ultrasonography LFT (normal)
Operation	ERCP (normal) Accessory right hepatic duct not seen CBD visibly intact and accessory duct divided Laparotomy CBD cholangiogram (no communication with cut duct)	
Recovery	Ligation of cut duct Uneventful	Temporary biliary fistula closed spontaneously
Follow-up	Well (5 years)	Well (3 years)

LFT, liver function testing; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

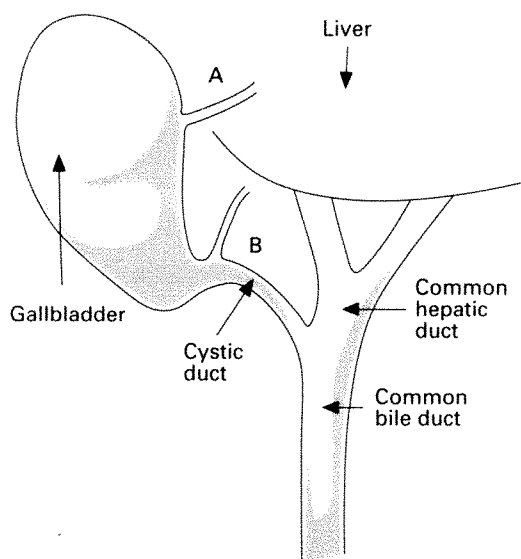


Fig. 4 Cholecystohepatic ducts (A and B) were noted and sacrificed in two patients

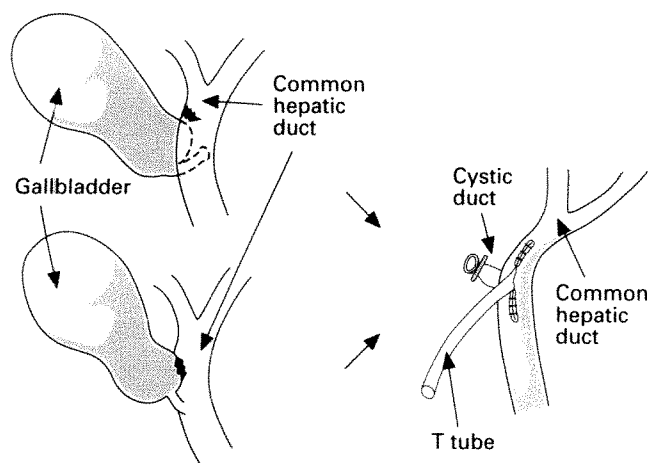


Fig. 5 Tears in the common hepatic duct in two patients. The tears occurred during dissection of Hartmann's pouch away from the duct

'Clip-induced' necrosis of the common bile duct–cystic duct junction

In one patient with a short cystic duct one of the clips used to occlude the cystic duct was placed at the junction with the CBD and in the postoperative period a biliary fistula ensued. ERCP failed for technical reasons and at laparotomy a T tube was placed in the CBD. The area of necrosis was pinpoint in size and the patient made an uneventful recovery. Operative cholangiography would not have prevented this injury.

Retained stones and other potential complications arising from the omission of operative cholangiography

Patients in this series were managed by selective preoperative ERCP, and operative cholangiography was not performed. To the authors' knowledge no existing bile duct pathology (stricture, ampullary lesion, etc.) was missed. The incidence of retained stones after laparoscopic cholecystectomy is the subject of a separate paper which reports a combined series with Hull Royal

Infirmery numbering 2038 patients. ERCP after surgery was required in 14 patients (0.7 per cent) for suspected stones and retained stones were actually found in ten (0.5 per cent)¹.

Discussion

Injury to the extrahepatic ducts has been one of the main causes for concern since the introduction of laparoscopic cholecystectomy². The role of routine operative cholangiography in the prevention of such injuries is controversial^{3–5}. Those surgeons who believe that operative cholangiography provides an essential safeguard against ductal injury should perform routine rather than selective cholangiography since injury can occur in seemingly straightforward operations.

However, audit of laparoscopic cholecystectomy in the West of Scotland over a 5-year period revealed that only 8.8 per cent of procedures included the use of operative cholangiography⁶. One ductal injury occurred during successful cholangiography. The authors noted that cholangiography did not play a part in the identification of bile duct injuries in their series. Macintyre and Wilson⁷ in a review of laparoscopic cholecystectomy noted that there was no evidence that routine cholangiography prevented major bile duct injury. Furthermore, they pointed out that operative cholangiography was not always possible, could be misinterpreted and was subject to observer variation. Misinterpretation of the cholangiogram was recorded as causing unnecessary laparotomy and occasional ductal injuries. Furthermore they warned that reliance on an operative cholangiogram could become a substitute for meticulous dissection. Gerber⁸ estimated that the practice of routine operative cholangiography would cost an extra \$200 million if applied throughout the USA and stated that the role of operative cholangiography in the prevention of injuries to the CBD 'is almost completely irrelevant'.

The present authors would favour early laparotomy if, despite meticulous dissection, ductal anatomy remained unclear. In this series laparoscopic cholecystectomy was performed without transection or stricture of the main extrahepatic duct system in 1200 patients. A safe dissection technique was used and intraoperative cholangiography was avoided. The authors have no experience of operative cholecystography. Although it can be argued that surgical trainees must be taught the technique of operative cholangiography, this argument alone does not justify the unnecessary routine use of the technique.

Injuries to accessory bile ducts during laparoscopic cholecystectomy have been recorded previously^{9–13}. In this series two patients had accessory right hepatic ducts which joined the cystic duct close to its junction with the gallbladder. These were not noted despite careful dissection and neither operative cholangiography nor ERCP demonstrated a communication between the accessory duct and the main duct system. Had operative cholangiography been performed before division of the cystic duct, the accessory duct would not have been detected as the cholangiogram catheter would have entered the cystic duct distal to the insertion of the accessory duct, which was not visible. Ligation of these accessory ducts resulted in one biliary fistula which arose when the ligature slipped. Closure of the fistula after 18 days justified conservative management in this patient. With greater experience such a complication would now

be treated by laparoscopic clipping of the transected accessory duct after performing operative cholangiography to demonstrate that the main duct system drained both lobes of the liver.

Cholecystohepatic ducts must be sacrificed in order to perform cholecystectomy. It is important to notice and clip such ducts if a biliary fistula is to be avoided. If a biliary fistula does occur and ERCP does not demonstrate any injury to the main extrahepatic duct system it is suggested that the fistula is likely to close spontaneously with simple abdominal drainage.

Dissection of an adherent gallbladder away from the bile duct may result in inadvertent entry into the bile duct. Two such instances are presented. Operative cholangiography would not have prevented these injuries. In both patients the main extrahepatic bile duct had been identified and the tears would probably have occurred during an open operation just as readily as during the laparoscopic procedure. In both patients a laparotomy was performed and a T tube was placed; recovery was uneventful. With greater experience a T tube would now be placed laparoscopically or a simple tear repaired with interrupted sutures.

One patient sustained necrosis at the junction of the CBD and cystic duct as a result of the placement of a clip in such a way as to render a tiny portion of the CBD ischaemic. A biliary fistula ensued and laparotomy was necessary only because a stent could not be passed endoscopically following diagnostic ERCP. The patient's recovery was uneventful but the message is clear. Clips on the cystic duct must not include a portion of the adjacent bile duct.

Routine operative cholangiography would not have prevented the injuries to the biliary tree encountered in this series. Unrecognized division of accessory ducts may explain some of the biliary fistulas reported in the literature. Such fistulas should be investigated by ERCP as soon as they are detected. Simple drainage of bile may be all that is required in the management of these fistulas if there is no communication between the divided accessory duct and the main biliary system.

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Risk factors linked to postoperative morbidity in patients with hepatocellular carcinoma

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Background The aim of this study was to clarify the risk factors for morbidity as well as to establish an optimum surgical strategy for hepatocellular carcinoma (HCC).

Methods The risk factors linked to postoperative complications were analysed in 388 patients over a 10-year period, according to the kind of operative procedure.

Results Stepwise regression analysis revealed that the most important factors related to postoperative morbidity were: age, creatinine level and the histological grade of fibrosis for the bisegmentectomy; the presence of diabetes mellitus, blood urea nitrogen level, the indocyanine green dye retention rate at 15 min and blood loss for the segmentectomy; the presence of diabetes mellitus and blood loss for subsegmentectomy; the presence of diabetes mellitus, the aspartate aminotransferase level, and the total operating time for resection less than subsegmentectomy.

Conclusion The most important risk factors were not always related to liver function tests, but instead to other coexisting conditions such as diabetes mellitus and operation stress including operating time and blood loss. Therefore, any future treatment strategy of hepatic resection for HCC should make every effort both to evaluate coexisting conditions carefully and to reduce operative stress as far as possible.

The liver has substantial regenerative ability and an immense reserve capacity. Seventy-five per cent of a healthy liver can be resected safely. Hepatocellular carcinoma (HCC) is the most common indication for hepatic resection in Japan and is usually associated with liver cirrhosis (approximately 80 per cent of cases). Patients with HCC are known to have the following specific characteristics: the frequent presence of liver cirrhosis, which limits the extent of hepatic resection, and frequent intrahepatic metastases via the portal vein, which necessitates a wider hepatic resection. In addition to liver disease itself, most patients with HCC have other pre-operative associated conditions such as coagulopathy, portal hypertension, peptic ulcer, biliary tract problems, diabetes mellitus and alcoholism. Therefore, hepatic resection for patients with HCC has tended to be one of the most dangerous operative procedures^{1,2}.

In the past decade, various kinds of improvement have led to decreased mortality and morbidity rates following hepatic resection^{3–8}. Most progress has been related to refined operative techniques, improved perioperative patient management and more sophisticated diagnostic modalities. However, the incidence of postoperative complications still remains high in comparison with other types of general surgery. Up to now, little has been documented regarding the risk factors for postoperative morbidity according to the operative procedure. However, the degree of the sudden decrease in functional liver mass and the development of postoperative portal hypertension after hepatic resection vary greatly according to the operative procedure used. Therefore an analysis based on operative procedure was considered important.

In this study, a 10-year experience of hepatic resection for HCC is reported. Furthermore, risk factors related to postoperative mortality and morbidity following hepatic

resection, as well as the development of strategies to reduce these problems, are discussed.

Patients and methods

A total of 410 patients underwent hepatic resection for HCC at Kyushu University Hospital during the 10-year period between April 1985 and March 1995. Twenty-two patients who had an emergency operation and transdiaphragmatic hepatectomy⁹ were excluded; thus a total of 388 patients was included in the study. Primary hepatic resection was performed in 354 cases, and repeat hepatic resection in 34. Operative procedures included trisegmentectomy (Hr3) in 13 patients, bisegmentectomy (Hr2) in 99, segmentectomy (Hr1) in 61, subsegmentectomy (HrS) in 72 and partial resection (Hr0) in 143. Hr3 represents either right lobectomy plus medial segmentectomy or left lobectomy plus anterior segmentectomy. Hr2 denotes either right lobectomy, left lobectomy or anterior and medial segmentectomies. Hr1 means resection of one of posterior, anterior, medial or left lateral segments. HrS denotes the systematic complete resection of a Couinaud's segment¹⁰. Hr0 indicates resection of less than a segment, such as wedge resection.

Regarding selection of operative procedure, the value of the indocyanine green dye retention test at 15 min (ICGR₁₅) has been considered the most important indicator of liver function, and thus the operative procedure has generally been selected according to the following criteria: Hr3, ICGR₁₅ below 15 per cent, Hr2, ICGR₁₅ below 25 per cent, Hr1, ICGR₁₅ below 35 per cent, HrS or Hr0, ICGR₁₅ below 45 per cent.

The incidence of death in hospital after hepatectomy was 11 (2.8 per cent) of 388 cases, and the operative mortality rate (defined as death within 30 days of operation) was four (1.0 per cent) of 388. The overall morbidity rate including mortality was 85 (21.9 per cent) of 388 patients studied. Morbidity in this study was defined as an event that prolonged the postoperative hospital stay by more than 1 month or which endangered the patient's life and/or necessitated reoperation. Morbidity consisted of liver failure in 16 patients, intractable ascites (which either had a poor response to ordinary diuretic therapy or required drainage due to tense ascites) as well as intractable

pleural effusion which required two or more thoracenteses or continuous drainage in 29, intraperitoneal infection in 27, intractable bile leak in seven, significant haemorrhage in two, gastrointestinal bleeding in one, ileus requiring reoperation in one, major enterocolitis in one, and serious respiratory failure in one.

To justify the above-mentioned principles for determining the operative procedure according to the ICGR₁₅ value, the risk factors related to postoperative morbidity were investigated among 39 detailed variables including the ICGR₁₅ value. In this study, caudate lobectomy, including partial resection of the caudate lobe, was defined as Hr0, as the volume of the resection was considered to be compatible with Hr0.

Some 310 patients with HCC who underwent primary curative hepatic resection during the same 10-year period were used to determine patient survival. Curative resection was defined as resection in which all the tumour could be resected macroscopically during operation.

Statistical analysis

The data were expressed as mean(s.d.). Analysis was carried out with Student's *t* test for continuous variables and the χ^2 test of independence for categorical variables. Next, stepwise multivariate regression analysis was performed using significant variables. In this study, 0.10 was considered significant for entering the variables into a stepwise regression model, in which an *F* value greater than 4.0 was considered as significant for determining a variable as a final independent one.

Results

Fig. 1 demonstrates the overall patient survival. The 3-, 5-, 7- and 10-year cumulative survival rates were 72.3, 53.2, 42.1 and 38.0 per cent respectively. The yearly postoperative morbidity rate is shown in Fig. 2. The high morbidity rate noted in 1985 has shown a dramatic decrease, although the rate has remained steady around 20 per cent.

Table 1 shows a comparison of the ICGR₁₅ value between patients with and without complications for each operative procedure. The mean value for each procedure was compatible with the preoperative criteria mentioned above, even though the ICGR₁₅ value in each group varied widely.

The postoperative morbidity rate after each operative procedure was as follows: Hr3, six of 13 patients; Hr2, 19 per cent; Hr1, 20 per cent; HrS, 29 per cent; Hr0, 20.3 per cent. For Hr3, no significant variable was found. For Hr2, higher age, the presence of oesophageal varices, the presence of hepatitis C virus (HCV), lower white blood cell count, lower platelet count, lower cholinesterase level and higher creatinine level were selected. For Hr1, a history of previous upper abdominal operation, the presence of diabetes mellitus, lower albumin level, lower bilirubin level, higher aspartate aminotransferase (ASAT) level, higher γ -globulin level, lower cholinesterase level, lower cholesterol level, higher blood urea nitrogen (BUN) level, higher ICGR₁₅ level, greater blood loss and operative procedure other than left lateral segmentectomy were selected. For HrS, lower age, the presence of diabetes mellitus, the presence of HCV, longer operating time and greater blood loss were selected. For Hr0, the presence of diabetes mellitus, higher bilirubin level, higher ASAT level, higher alanine aminotransferase level, higher γ glutamyl transpeptidase level, longer operating time, greater blood loss and caudate lobectomy were selected.

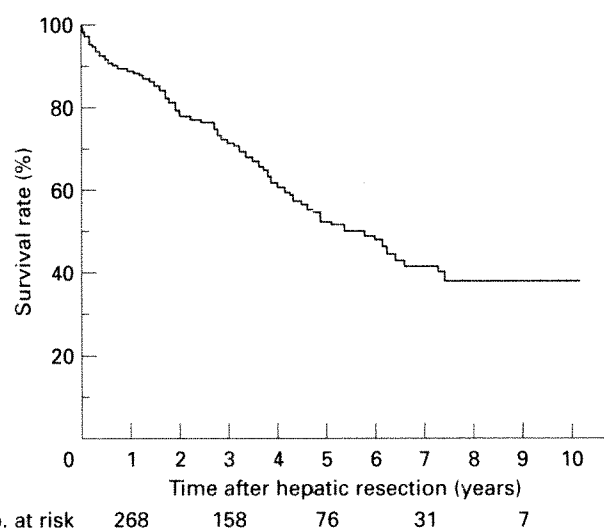


Fig. 1 Overall survival of patients with hepatocellular carcinoma, including hospital deaths

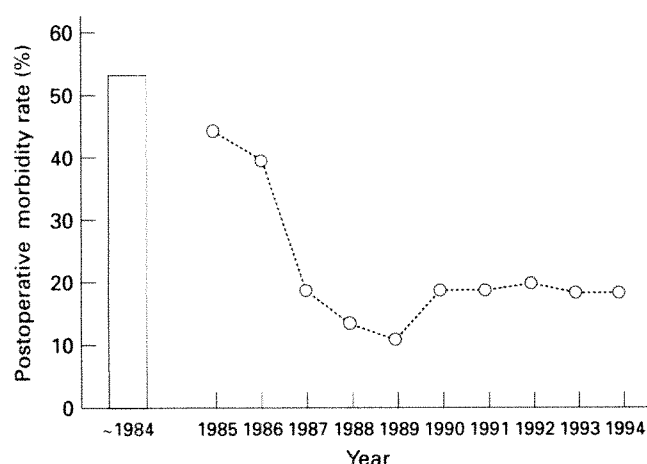


Fig. 2 Yearly change in the postoperative morbidity rate of patients with hepatocellular carcinoma. Postoperative morbidity has decreased in comparison with that before 1984. However, the recent incidence of major complications after hepatic resection remains at around 20 per cent. The number of patients developing a severe postoperative complication was seven, six, seven, five, three, 11, 11, 13, 11 and 11 for years 1985–1994 respectively

Table 1 Comparison of indocyanine green dye retention test values at 15 min between patients with and without postoperative complications for each operative procedure

Operative procedure	ICGR ₁₅ (%)	
	Without morbidity	With morbidity
Hr3 (n = 13)	13.7 (6.8–28.8)	13.3 (5.5–27.7)
Hr2 (n = 96)	12.6 (1.0–28.0)	15.1 (5.6–26.4)
Hr1 (n = 62)	15.4 (4.4–39.9)	22.6 (6.4–52.3)
HrS (n = 70)	19.1 (2.4–53.4)	18.8 (1.7–48.1)
Hr0 (n = 147)	20.2 (3.8–65.3)	22.1 (0.3–50.7)

Values are mean (range). ICGR₁₅, indocyanine green dye retention rate at 15 min. Operative procedures are defined in the text

Table 2 Significant variables determined by a stepwise regression model for each operative procedure

Procedure	Variable	Coefficient	F
Hr2	Age (years)	0.011	6.906
	Creatinine (mg/dl)	0.066	4.174
	Cirrhosis	0.151	8.493
Hr1	Diabetes mellitus	0.249	4.896
	BUN (mg/dl)	0.011	7.254
	ICGR ₁₅ (%)	0.011	5.292
	Blood loss (ml)	8.043×10^{-5}	11.392
HrS	Diabetes mellitus	0.232	4.255
	Blood loss	9.924×10^{-5}	8.033
Hr0	Diabetes mellitus	0.153	4.534
	ASAT (units/l)	1.868×10^{-3}	4.464
	Operating time (min)	1.160×10^{-3}	9.851
All procedures	ASAT (units/l)	7.098×10^{-4}	5.310
	BUN (mg/dl)	6.913×10^{-3}	9.479
	Operating time (min)	8.635×10^{-4}	9.851

ASAT, aspartate aminotransferase; BUN, blood urea nitrogen; ICGR₁₅, indocyanine green dye retention rate at 15 min. Operative procedures are defined in the text

Table 2 demonstrates the results of a stepwise multivariate regression analysis, including the correlation coefficient of the model and risk factors. Significant independent risk factors for all operative procedures were found to be ASAT level, BUN concentration and operating time.

Discussion

When determining the operative procedures to be undertaken the ICGR₁₅ value has been one of the most important conditions; furthermore, the following conditions were also taken carefully into consideration: size of the HCC, location of the tumour with respect to such factors as depth and distance from major vessels, the degree of advancement of HCC such as vascular invasion and intrahepatic metastases, as well as the patient's general condition. However, in reality, actual selection of the operative procedure is based primarily on the personal experience of the hepatic surgeon.

Mortality and morbidity rates in other centres have been reported to range from 6.0 to 10.5 per cent^{3,5,7} and from 20.1 to 32.0 per cent^{3,7} respectively. In comparison to these results, the present rates of 2.8 per cent for hospital death and 21.9 per cent for morbidity are excellent. Liver failure after hepatic resection is the most serious complication in cirrhotic patients with HCC; therefore, an analysis targeting liver failure is considered important. In this 10-year experience, only 16 (4.1 per cent) of 388 patients had postoperative liver failure, although the number of patients was too small to make any definite conclusion about the risk factors involved. Therefore, the present study was done using significant postoperative complications including death. A decreased morbidity rate in the modern era has been reported previously^{8,11}; therefore, the aim of this investigation was to elucidate more detailed information relating to this morbidity. Major hepatic resection for HCC has been reported to result in a high hospital mortality rate⁶; however, in this study the morbidity rate for Hr2 and Hr3 was 25 (22.3 per cent) of 112, which is similar to the overall morbidity rate of 21.9 per cent. This is probably due to the policy of

patient selection as well as improved perioperative management, including operative techniques.

An ICGR₁₅ value of less than 14 per cent has been reported to be best for distinguishing between patients with and without postoperative morbidity following major hepatic resection⁶. In the authors' institution, an ICGR₁₅ value of less than 20 per cent and portal pressure of less than 200 mmH₂O has been considered a safe limit for Hr2¹². The significance of either the liver function scoring system^{1,5} or the redox tolerance test¹³ has been reported. In this study, almost all liver function test results such as lecithin:cholesterol acyltransferase concentration which has been advocated as a useful indicator of liver function^{14,16}, were evaluated in detail. However, in the multivariate analysis, parameters other than liver function were finally selected, such as diabetes mellitus and blood loss. This suggests that the selection criteria for the operative procedures have been satisfactory to some extent.

The present study clearly revealed that coexisting conditions such as diabetes mellitus, as well as operative stress including operation time and blood loss, are extremely important risk factors. Therefore, any future treatment strategy should make every effort both to evaluate coexisting conditions carefully and to reduce operative stress as far as possible. For Hr2, patients over 70 years of age have been reported to be at relatively high risk for postoperative liver failure¹⁷; therefore, the authors' recent policy for elderly patients is to undertake a smaller resection.

For Hr1, diabetes mellitus, renal dysfunction, blood loss and ICGR₁₅ value were important risk factors. Diabetes mellitus is a well known risk factor after major surgery because of the susceptibility to infection; furthermore, diabetes impairs hepatic regeneration and decreases hepatic intracellular energy status after partial hepatectomy in rats¹⁸. This fact is considered to be one of the most important reasons why pre-existing diabetes mellitus is associated with major complications following hepatic resection. Furthermore, patients with diabetes mellitus have an increased risk of postoperative complications¹⁹. Stricter preoperative control of diabetes mellitus has also been advocated for improved results²⁰.

Regarding renal dysfunction, preoperative renal dysfunction with high levels of BUN contributed to the development of major complications such as intractable pleural effusion and ascites, because the renal dysfunction limited diuretic therapy for ascites and pleural effusion. Some patients had to undergo peritoneovenous shunting with a Denver shunt tube.

For Hr1, ICGR₁₅ itself, which is the most important factor for determining the operation procedure, was selected as a significant risk factor. A more careful assessment of liver function test results, including a volumetric study, is therefore recommended. Furthermore, this evidence suggests that, for Hr1 the criterion of an ICGR₁₅ value of less than 35 per cent is not pertinent, as one determinant of liver function alone is not sufficient to indicate the optimal operative procedures clearly.

Regarding the yearly changes in morbidity, it is of interest that the later morbidity rate continued to remain at around 20 per cent, and that the types of morbidity have also remained unchanged. Substantial clinical progress has recently been made, and the role of prostaglandin, coagulation and fibrinolytic systems in hepatic resection has also been investigated thoroughly²¹⁻²³. Further investigation into the causes of complications, as

well as the development of effective strategies to prevent them, are called for to obtain better results for hepatic resection in cirrhotic patients with HCC than those observed in the past 10 years.

In conclusion, the most important risk factors linked to significant postoperative complications are not always related to liver function, but appear to be associated with other coexisting conditions such as diabetes mellitus or operative stress, including operating time and blood loss. Therefore, any future treatment strategy of hepatic resection for HCC should make every effort both to evaluate coexisting conditions carefully and to reduce operative stress as far as possible.

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Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer

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Background In a randomized double-blind study the efficacy of neurolytic coeliac plexus block (NCPB) was compared with pharmacological therapy in the treatment of pain from pancreatic cancer.

Methods Twenty-four patients were divided into two groups: 12 patients underwent NCPB (group 1) and 12 were treated with pharmacological therapy (group 2). Immediate and long-term efficacy, mean analgesic consumption, mortality and morbidity were evaluated at follow-up. Statistical analysis was performed with the unpaired *t* test, Mann–Whitney *U* test and Fisher's exact test.

Results Immediately after the block, patients in group 1 reported significant pain relief compared with those in group 2 ($P < 0.05$), but long-term results did not differ between the groups. Mean analgesic consumption was lower in group 1. There were no deaths. Complications related to NCPB were transient diarrhoea and hypotension (P not significant between groups). Drug-related adverse effects were constipation (five of 12 patients in group 1 versus 12 of 12 in group 2), nausea and/or vomiting (four of 12 patients in group 1 versus 12 of 12 in group 2) ($P < 0.05$), one gastric ulcer and one gluteal abscess in group 2.

Conclusion NCPB was associated with a reduction in analgesic drug administration and drug-related adverse effects, representing an effective tool in the treatment of pancreatic cancer pain.

Despite possible treatment by surgical operation, radiation therapy and chemotherapy, the prognosis of pancreatic cancer is poor^{1–4}. Thus the control of symptoms related to pancreatic cancer and its evolution represents a primary goal for the treatment of most patients affected by this disease^{5–8}.

Pain is frequently present in the early stages of the disease⁹. It often changes from an upper abdominal visceral pain at the beginning to acquire new characteristics and localization during the course of the disease^{10,11}.

To date, different approaches have been suggested for treatment of pancreatic cancer pain, including pharmacological¹², radiation³, neuroinvasive¹¹ and neurolytic treatments^{13–17}. Some authors consider the use of the neurolytic coeliac plexus block (NCPB) to be optimal^{6,15,16,18,19}. This technique has been used for many years in the treatment of pain caused by upper abdominal malignancy¹⁹. Although the role of this technique has been established in the literature²⁰, few controlled trials have compared its efficacy with that of other types of treatment²¹.

The aim of this prospective randomized double-blind study was to compare the efficacy of NCPB with pharmacological therapy in the treatment of pain in patients with pancreatic cancer.

Patients and methods

The study was conducted on 24 patients (17 men), aged 27–76 years, affected by irresectable pancreatic adenocarcinoma and referred to the authors' pain relief centre between October 1991 and June 1993. Histopathological diagnosis was obtained by means of ultrasonographically guided needle aspiration cytology.

Following informed consent, patients were placed randomly in one of the following groups: in group 1, 12 of the 24 patients underwent NCPB with the Boas technique²²; in group 2, 12 patients were treated with pharmacological therapy and an anaesthetic coeliac plexus block.

In group 1, the patients, after premedication with atropine, were placed in the prone position. The needles (spinal needle quincke type point 18 G; Becton Dickinson, Franklin Lakes, New Jersey, USA) were positioned under fluoroscopic monitoring with an image intensifier and under local anaesthesia with 1 per cent mepivacaine. After verifying correct placement of the needle and spread of contrast medium (2–4 ml of 50 per cent meglumine iotalamate 400 mg/ml diluted with 1 per cent mepivacaine via each needle) in the target area by fluoroscopy, an anaesthetic test was performed injecting 2 per cent mepivacaine with 1:200 000 adrenaline, 6–8 ml via each needle. After assessing the efficacy and safety of this test, 7 ml of absolute alcohol was injected via each needle 30 min later.

In patients in group 2 the anaesthetic coeliac plexus block, using the same technique, injecting 2 per cent mepivacaine with adrenaline 1:200 000, 6–8 ml via each needle, was performed. It was decided to perform such a block in the control group to assess pain relief of longer duration than that expected with the local anaesthetic block²³.

Neurolytic and anaesthetic blocks were performed by one operator who was not involved in patient follow-up.

Drug therapy was conducted according to World Health Organization guidelines²⁴ using diclofenac sodium as first-choice non-steroidal anti-inflammatory drug (NSAID). Opioid administration was conducted according to the criterion of opioid responsiveness²⁵ requiring opioid dose escalation until adequate analgesia was achieved or intolerable side-effects were experienced.

Pain quality and quantity were evaluated by means of the Arner and Arner pain classification²⁶ and the Scott–Huskisson visual analogue score (VAS)²⁷ respectively. At the time of enrolment, all patients reported the presence of visceral coeliac-type pain, localized to the upper abdomen, epigastrium and sometimes to the left or right hypocondrium, often radiating to the back like a band and perceived by the patient as deep rather than superficial, and frequently accentuated by palpation. The

pain may be chronic rather than episodic (continuous visceral pain) or with the characteristics of colic-type pain occurring especially after meals (intermittent visceral pain)²⁰.

All patients were treated with drug therapy as outlined above. Nine of 12 patients in group 1 and eight of 12 in group 2 were treated with NSAIDs, whereas three patients in group 1 and four in group 2 were treated with NSAIDs and opioids.

The mean(s.d.) interval elapsing between the occurrence of pain and treatment was 4.6(1.6) (range 2–7) months in group 1 and 4.9(1.7) (range 3–7) months in group 2.

After the block the patients were hospitalized for a 3-day period and were then discharged.

Follow-up was conducted until death, with daily visits during hospital admission and then regular assessment by telephone, or by office visits at least twice a week by physicians blinded to the treatment group. The following parameters were evaluated: (1) immediate (24–48 h) and long-term efficacy of the treatment until death – complete pain relief was the total absence of pain (VAS 0), partial pain relief was reduction in pain intensity of at least three points in the VAS, and no pain relief was the persistence of unmodified pain; (2) mean consumption of analgesic drugs at one-quarter, one-half and three-quarters of the survival time after treatment and on the day before death; (3) deaths and complications of the procedure and of the disease.

Statistical analysis of results was performed with an unpaired *t* test for continuous variables and with Fisher's exact test for categorical variables. Pain scores were compared with the Mann–Whitney *U* test. Differences were considered significant when $P < 0.05$.

Results

No statistically significant difference was observed between the two groups in age, mean analgesic drug consumption before treatment, mean interval elapsing between the onset of pain and commencement of treatment, and mean survival time of patients after treatment (Table 1). The median value of the preoperative pain intensity reported by patients on a VAS from 0 to 10 was 7.5 (range 6–10) in group 1 and 7 (range 6–9) in group 2 (P not significant).

After a 24-h interval from the start of treatment in group 1, nine patients achieved complete pain relief; three reported the persistence of residual pain. In all these cases the pain was described as a localized, superficial, sharp pain accentuated by palpation of intercostal spaces (somatic pain), whereas visceral coeliac-type pain had disappeared. At 24 h, two patients in group 2 had achieved complete pain relief whereas ten reported the persistence of residual pain of the same type and site as that described before performance of the block. The difference between groups was statistically significant ($P < 0.05$).

After a 48-h interval the results were unchanged in group 1, but in group 2 all patients reported the persistence of visceral coeliac-type pain ($P < 0.05$).

During follow-up two patients in group 1 reported the recurrence of visceral coeliac-type pain and six reported pain of different type and site. Complete pain relief until death was achieved in one patient with NCPB alone and in nine in whom the block was combined with drug therapy; two patients reported only partial pain relief despite drug therapy. In group 2, drug therapy produced complete pain relief until death in seven patients and partial pain relief in five (P not significant).

Table 2 provides data for mean consumption of diclofenac sodium and opioids (expressed as oral morphine equivalents). Consumption of diclofenac sodium was significantly lower at all intervals in group 1 compared with group 2. Mean consumption of opioids was also

Table 1 Characteristics of the patients studied

	Group 1	Group 2
Age (years)	57(11.5)	60(10.1)
Analgesic drug consumption (mg/day)		
Diclofenac sodium	140(43)	140(93)
Oral morphine equivalents	10(18)	11(17)
Interval between pain occurrence and treatment (months)	4.2(1.5)	4.4(1.6)
Survival time after treatment (days)	102(31)	101(37)

Values are mean(s.d.)

Table 2 Consumption of diclofenac sodium and opioids (oral morphine equivalents)

	Group 1	Group 2
Diclofenac sodium (mg/day)		
At one-quarter of survival time	87(54)	165(53)*
At one-half of survival time	98(63)	171(45)*
At three-quarters of survival time	106(50)	175(45)*
Day before death	119(54)	179(45)*
Opioids (mg/day)		
At one-quarter of survival time	14(15)	36(15)*
At one-half of survival time	30(17)	58(25)*
At three-quarters of survival time	47(42)	76(42)
Day before death	59(44)	92(51)

Values are mean(s.d.). * $P < 0.05$ (group 2 versus group 1, unpaired *t* test)

lower in group 1 than in group 2, but the difference was significant only at one-quarter and one-half, not at three-quarters, of the survival time, nor at death of the patients.

The following complications related to the blocks were recorded: transient diarrhoea (1–3 days) in three patients in group 1 and in two in group 2; transient orthostatic hypotension (systolic blood pressure less than 33 per cent of basal value) in five patients in group 1 and in two in group 2. These differences were not significant.

There was no operative mortality or complication related to performance of the block.

Adverse effects associated with drug therapy were constipation in five patients in group 1 and in all in group 2; nausea and/or vomiting in four patients in group 1 and in all in group 2; bleeding NSAID-related gastric ulcer (documented endoscopically) in one patient in group 2; and a gluteal abscess at the site of injection in one patient in group 2. The incidence of constipation and nausea and/or vomiting was significantly lower in group 1 than in group 2.

Discussion

Although some authors have suggested that it is not possible to define clearly the role of NCPB in the treatment of pancreatic cancer pain^{8,28}, recent prospective randomized controlled studies have highlighted some important factors: NCPB abolishes pain until death in 10–24 per cent of patients when employed alone and in 80–90 per cent when associated with other kinds of

treatment²⁰; early performance of the block is more efficacious than late performance^{20,29}; opioid consumption until death is lower in patients with pancreatic cancer who have undergone NCPB²¹; and survival time is improved in those treated with alcohol splanchnicectomy compared with placebo²⁹.

Analysis of the data of this prospective randomized double-blind study demonstrates that NCPB abolished visceral coeliac-type pain in all treated patients 24 and 48 h after its performance and in ten of the 12 patients until death, and that in the course of the disease the treatment provided complete pain relief in only one of 12 patients if used alone and in a further nine patients if associated with drug therapy. This finding could be related to the fact that pancreatic cancer pain rarely remains of visceral coeliac type in the far advanced stages of the disease, often acquiring several characteristics and sites because of the neoplastic involvement of somatic or nervous structures³⁰.

Although the success rate was not significantly higher than in the pharmacological group, mean consumption of analgesic drugs, both diclofenac sodium and opioids, at the intervals examined was lower in patients treated with NCPB than in the pharmacological group. The partial difference with other authors' data²¹ could be ascribed to the longer survival after performance of the treatment in the present population.

There were no deaths due to the block, and complications were reversible and easy to treat. The incidence of adverse effects related to the analgesic drug therapy was lower in the group of patients treated with NCPB, suggesting that the reduction in analgesic consumption is of real clinical benefit.

In conclusion, NCPB, by abolishing visceral coeliac-type pain in a high proportion of patients with negligible sequelae, permits the reduction of analgesic drug consumption and consequently a reduction in the occurrence of drug-related adverse effects. Thus, NCPB represents an effective tool in the treatment of pancreatic cancer pain. Nevertheless, further controlled studies on larger populations are needed to clarify its impact on patients' quality of life compared with other kinds of treatment.

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Blood supply of the right and left hepatic ducts

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Background Increasing precision of liver resection and use of reduced liver grafts stimulated this study of the blood supply of the intrahepatic bile ducts.

Method Corrosion casts of human liver were dissected to study the blood supply of the right and left hepatic ducts.

Results The dissected casts showed that the ducts are surrounded by a vascular plexus supplied from the main right and left hepatic arteries, segmental arteries, gastroduodenal artery and accessory hepatic arteries. This plexus is closely associated with the arteries supplying the caudate lobe. They arise from both right and left in two general patterns. This plexus links the arterial supplies of the right and left livers. Segment IV and the central portion of the left hepatic duct are often supplied by the right arterial system.

Conclusion This study provides further insights into bile duct blood supply. The caudate lobe and biliary plexus provide collateral connections between the right and left livers.

Biliary complication rates of up to 50 per cent in the pioneering series of orthotopic liver transplantation^{1,2} have ensured enduring respect for the details of biliary reconstruction which is regarded as the major technical challenge of the transplant procedure. Recognition of the importance of an adequate blood supply to the donor bile duct³ and clarification of the anatomy of the blood supply of the common bile duct⁴ were fundamental to the development of various improvements in techniques for biliary reconstruction^{3,5–7}. The observation of an association between biliary complications and thrombosis of the hepatic artery^{6,8,9} lent support to this belief that ischaemia of the bile duct was an important factor contributing to the development of anastomotic and non-anastomotic strictures and anastomotic leaks. Despite various improvements, biliary complication rates of up to 34 per cent¹⁰ continue to be reported and ischaemia of the bile duct remains an important factor contributing to the development of many biliary complications after liver transplantation¹¹. Bile duct ischaemia is also relevant in some iatrogenic common bile duct strictures which result from injury to the ascending branches of the gastroduodenal artery, the chief blood supply of the common bile duct¹², with or without concomitant injury to the right hepatic artery. Strictures and leaks from biliary–enteric anastomoses after right and left extended liver resection may also be related to bile duct ischaemia.

The shortage of donor organs of suitable size for children with end-stage liver disease has, to some extent, been overcome by using reduced-size adult liver allografts^{13–15}. The risk of hepatic artery thrombosis appears to be lower with reduced liver transplant than with whole liver paediatric transplant¹⁶. However, when one adult cadaver liver is split into two grafts for separate patients or a left lateral sector is transplanted from a living related donor^{17–22}, the complexity of the liver resection is greatly increased and the margin for error is considerably

reduced. For such resections detailed knowledge and understanding of the anatomy is essential.

This study aimed to define the blood supply to the main intrahepatic bile ducts (IBDs) to determine whether there are areas at particular risk in preparing these types of liver grafts and, indeed, in non-transplant hepatobiliary surgery and, if so, to provide anatomical information that might help to avoid compromising the blood supply of the IBDs.

Materials and methods

Human livers were removed, within 24 h of death, from cadavers of people under the age of 35 years who had died from head or chest trauma. The livers were carefully dissected and removed *en bloc* with the biliary system, duodenum, head of pancreas and anterior part of the suprarenal abdominal aorta.

Semiopaque plastic cannulas were firmly tied into the coeliac artery and portal vein, and cold Ringer's lactate solution was flushed through the liver until the effluent from the hepatic veins and inferior vena cava was almost clear. Any leaks were carefully ligated.

Batson's no. 17 anatomical corrosion compound (Polysciences, Warrington, Pennsylvania, USA) was prepared in the following proportions: 100 parts monomer base with added pigment, ten parts catalyst and one part promoter. Differently coloured preparations were then injected into the portal vein and coeliac artery (and in some specimens into the biliary system). The most satisfactory casts were produced when the portal venous system

Table 1 Coding system developed to identify the various extrahepatic and intrahepatic arteries

Arabic numerals

- 1, Common hepatic artery
- 2, Gastroduodenal artery
- 3, Proper hepatic artery
- 4, Right hepatic artery
- 5, Left hepatic artery
- 6, Accessory right hepatic artery from superior mesenteric artery
- 7, Accessory left hepatic artery from left gastric artery

Upper-case letters

Major branches of main arteries (e.g. segmental branches)

Lower-case letters

Main arterial branches entering the peribiliary plexus

Preliminary data presented to the 1991 meetings of the Surgical Research Society of Southern Africa and the South African Gastroenterological Society, and the World Congress of HPB Surgery in Hong Kong, 1992

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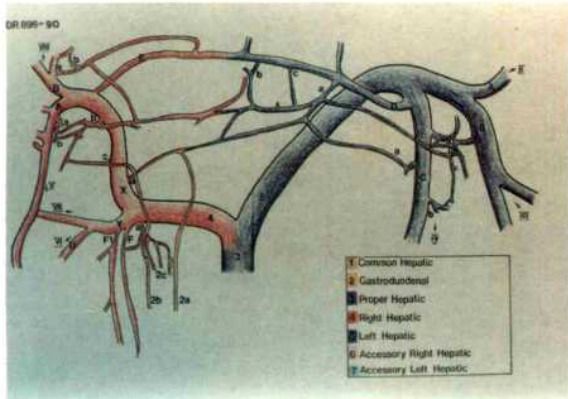


Fig. 1 Dissected corrosion cast, DR896. The specimen has only proper hepatic artery (PHA) and intrahepatic branches. This liver has conventional arterial anatomy with PHA dividing into right hepatic artery (RHA) and left hepatic artery (LHA). The RHA divides into posterolateral and anteromedial trunks which each divide into their respective segmental arteries. Two separate cystic arteries arise from the posterolateral trunk of the RHA. The LHA divides into segmental arteries for segments II, III and IV. The caudate lobe has an 'arcade' type supply with branches (D and E) from both sides joining each other. The hepatic duct plexus in the centre receives branches from major divisions of the RHA and LHA, segmental arteries and the caudate arcade artery. It is also in direct contact with the main common bile duct arteries (2a-c)

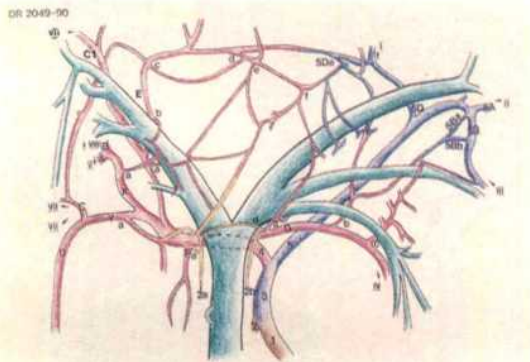


Fig. 2 Dissected corrosion cast, DR2049. In this case the bile duct was also cast with green resin. The artery to segment IV, G, arises from the right hepatic artery. The left hepatic artery divides into segment II and III arteries and the caudate 'arcade' artery

was first partially filled with approximately 90–100 ml (for adult livers) of resin mixture and then the artery was injected until the small arteries of Glisson's capsule were seen to fill with resin.

The specimen was stored on crushed ice in a refrigerator at 4°C for 18–24 h to allow slow curing of the resin. The specimen was then placed in a solution of potassium hydroxide at 50°C until all the tissue had corroded leaving only the vascular cast; this took 3–5 days. The vascular cast was gently cleaned with water and dissected under an operating microscope to expose the vascular cast of the main IBDs. The venous components of the IBD casts were carefully removed to leave behind the arterial part of the plexus.

Diagrams of the dissections were sketched (Figs 1–6) and a coding system (Table 1) was devised with each of the main arteries allocated a different colour, and each major branch of the main arteries an upper-case letter. Each arterial branch

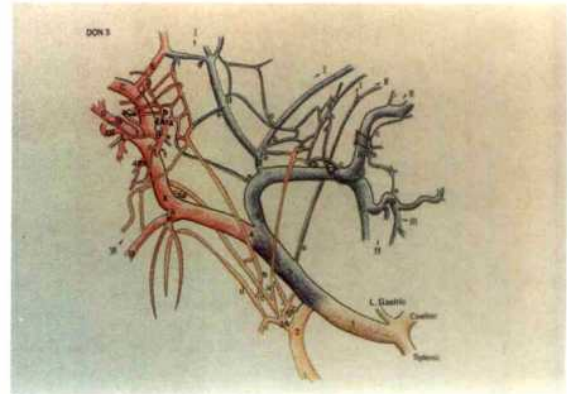


Fig. 3 DON3, an excellent cast made from the liver of an organ donor. Branches from the gastroduodenal artery to the common bile duct (2Aa, b, c, d) clearly communicate with the intrahepatic biliary plexus. There is a very clear 'tree' pattern of supply to the caudate lobe with a short branch from the left hepatic artery (5D) bifurcating to supply different parts of the caudate lobe and giving off several branches to the biliary plexus. There is an unusual accessory artery arising from the proper hepatic artery (3a) to supply segment II and the caudate separately

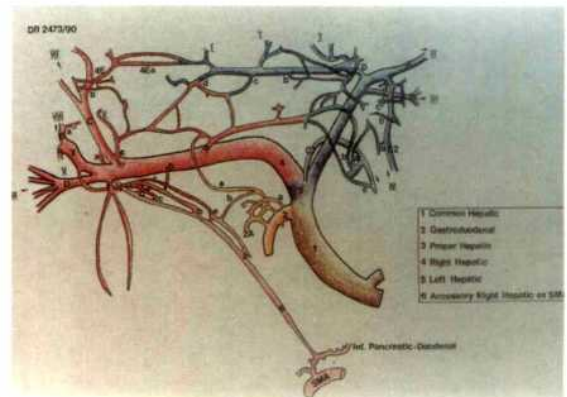


Fig. 4 Very good quality cast, DR2473, with excellent definition of detail. The liver had conventional vessels from the coeliac axis as well as an accessory artery from the superior mesenteric artery (6). The plexus around the common bile duct is supplied by branches from both the gastroduodenal artery and the accessory right hepatic artery. The caudate has an 'arcade' type supply with a larger branch from the left (5D) anastomosing with several smaller branches from the right. There is a fairly large artery, which arises from the right hepatic artery, supplying the biliary plexus of the hepatic ducts. Segment IV is supplied by two arteries: C1 arising from the proper hepatic artery at its bifurcation and C2 branching from the segment II artery

entering the IBD plexus from a major coded artery was allocated a consecutive lower-case letter and colour which corresponded with the colour of its parent artery.

Results

Nine corrosion casts, produced after developing the technique described above, were of sufficiently good quality to permit detailed analysis (Fig. 7).

Extrahepatic arterial supply

Six livers had a conventional common hepatic artery dividing into the main right and left hepatic arteries (Fig.

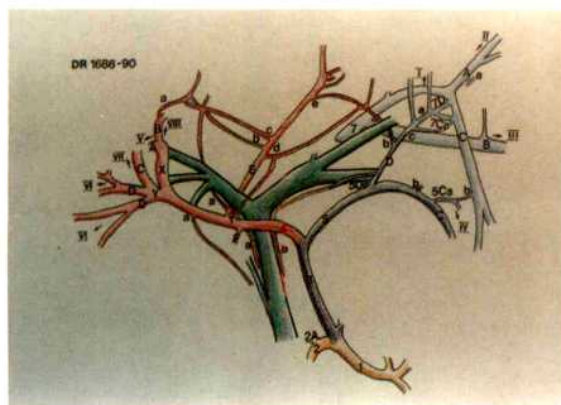


Fig. 5 Dissected corrosion cast of liver, DR1686, in which the bile duct was injected. Segments II and III are supplied predominantly from a branch of the left gastric artery. The proper hepatic artery divides into the right hepatic artery (RHA) and a left hepatic artery which supplies segment IV and anastomoses with the left gastric artery branches. The posterolateral trunk of the RHA trifurcates into two branches to segment VI and one to segment VII. The anteromedial trunk bifurcates distally into two short segmental branches for segments V and VIII. The caudate is supplied in a 'tree' pattern by a branch of the main RHA which gives branches to the biliary plexus, which also receives branches from segmental arteries of each side

1). However, in two of these the segment IV artery arose from the main right hepatic artery (Fig. 2), in another there was an accessory artery to segments I and II arising from the common hepatic artery proximal to the main bifurcation (Fig. 3) and another had an accessory branch to segment II arising from the mid common hepatic artery. One liver had an accessory artery from the superior mesenteric joining the right hepatic artery and supplying the right liver and common bile duct (Fig. 4). The last two had major supply to segments II and III from the left gastric artery. In one of these there was a fairly substantial left hepatic artery supplying segment IV and a small accessory branch to the rest of the left liver (Fig. 5). The other had a small branch to segment IV arising quite proximally on the common hepatic artery and additional branches to segments IV and I arising from the right hepatic artery (Fig. 6).

Intrahepatic distribution of the hepatic arteries

The right hepatic artery had a variable pattern of termination: in three livers it bifurcated into anteromedial and posterolateral sector trunks, each of which bifurcated further distally into the segmental branches (Figs 1 and 2), and in four livers it trifurcated into segment VI and VII arteries and a medial sector trunk which bifurcated further out (Fig. 4). In the remaining two livers the segment VI artery branched from the main right hepatic artery which continued for a few centimetres before dividing into the segment VII artery and the medial sector trunk (Fig. 3).

Caudate lobe

In all casts the caudate received branches from both right and left but the patterns differed. Two main patterns were recognized, an 'arcade' pattern and a 'tree' pattern. In the arcade pattern, which was recognized in four dissected

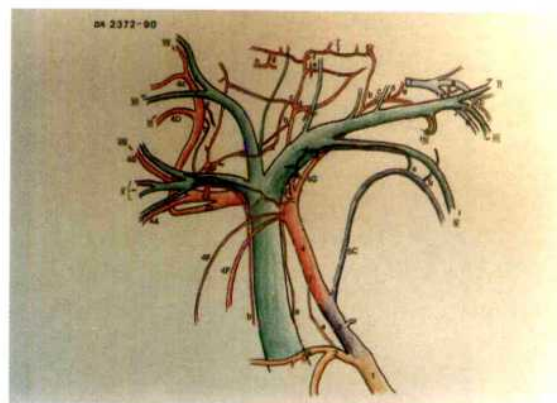
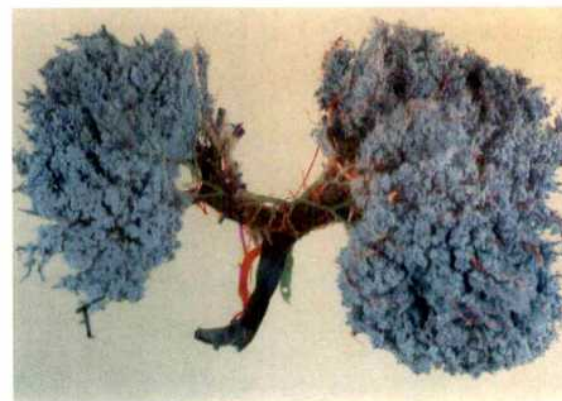


Fig. 6 This cast, DR2372, in which the bile ducts were also injected, shows some unusual intrahepatic arterial anatomy. Segment IV is supplied by a small branch from the proper hepatic artery (5C) and another from the right hepatic artery (RHA) (4G). Segments II and III are supplied by a branch of the left gastric artery. The caudate lobe is supplied predominantly in a 'tree' pattern by a branch arising from the RHA (4E)



a



b

Fig. 7 Posterior views of two dissected casts (right liver is on the right). The portal vein is blue and the hepatic artery is red. Segment I and parts of segments IV, V and VIII have been removed to expose the vascular plexus around the confluence of hepatic ducts. The position of the bile ducts (green) is clearly shown in a and corresponds with the position of the arterial plexus seen more clearly in b which does not have resin in the bile ducts

casts, the caudate lobe arterial supply consisted of an artery that ran along the cranial aspect of the hepatic duct confluence (Figs 1, 2 and 4) and represented a fusion of vessels of similar size arising from the distal parts of the left hepatic and the central branches of the right hepatic artery. In addition to giving branches to the caudate, the arcade artery gave several branches to the hepatic duct plexus.

In the tree pattern, which was recognized in the other five livers, the caudate lobe was supplied by a single main artery arising centrally, either from the proximal right hepatic artery (Figs 5 and 6) or from the left hepatic artery (Fig. 3), and giving branches to right and left. It passed behind the main left or right hepatic duct and in each case had clearly recognizable connections with the right and left segmental branches and the hepatic duct plexus.

Unlike the arterial supply, the portal venous supply to the caudate lobe was generally by several short vessels that passed posterior to the bile ducts, directly to the caudate lobe from the main left and right portal veins.

Main hepatic ducts

The dissected casts demonstrate that the extrahepatic and IBDs are surrounded by a vascular plexus (Fig. 7) which is composed of branches arising directly from right and left hepatic arteries (and accessory hepatic arteries when present) and their segmental branches, and indirectly from the gastroduodenal artery via the arteries supplying the common bile duct (Figs 1–6). It must be emphasized that the plexus around the right and left hepatic ducts is continuous with a similar plexus surrounding the common bile duct and common hepatic duct. This intrahepatic plexus was always closely associated with the arterial supply of the caudate lobe. Venous drainage from the plexus was into the portal veins and it was also evident that there is a dense complex of lymphatic vessels within the vascular plexus.

Discussion

Modern hepatic surgery has developed largely as a result of the anatomical observations of Couinaud²³ who noted that each liver comprises eight segments with an independent arterial and portal venous supply and biliary drainage. From these observations it was suggested that the right and left livers were largely independent of each other. However, Bismuth²⁴ pointed out that the caudate lobe (segment I) receives branches from both right and left branches of portal vein and hepatic artery, and its veins drain directly into the inferior vena cava. The present authors' dissections confirm that the caudate lobe derives its arterial and portal venous supply from both left and right sides of the liver and should thus be regarded as a segment shared by the left and right livers.

The great variability of the extrahepatic pattern of arterial supply of the liver is well recognized^{25–27} and the authors' analysis of corrosion cast dissections re-emphasizes this; it also draws attention to the variability of the intrahepatic arteries, particularly those of segment IV. Its artery took origin from the right hepatic artery in two of the six livers with 'conventional' extrahepatic arterial supply. Furthermore, in the two livers that had dominant supply to segments II and III from left gastric artery, segment IV was supplied by a single large branch of the proper hepatic artery (left hepatic artery) in one and, in

the other, by two branches, one from the proper hepatic artery and one from the right hepatic artery.

The role of the artery and its relationship with the portal vein in the hepatic lobules is now more clearly understood²⁸. However, the authors' dissections of vascular corrosion casts of human livers clearly show that the IBDs are surrounded by a vascular plexus which is derived from branches of the hepatic arteries and their segmental branches, and it is clear that a very important function of the hepatic arteries is the nourishment of the bile ducts. The arterial supply to the common bile duct is known to be derived predominantly from two branches of the gastroduodenal artery⁴, but these dissections show that there is a vascular plexus surrounding the whole biliary system. The plexus around the intrahepatic ducts, being in direct continuity with the plexus around the common bile duct, represents an important connection between the hepatic arteries, via the common duct arteries, and the gastroduodenal artery. This must therefore represent an important collateral source of arterial supply to the liver in the event of occlusion of the hepatic artery.

The close association of the peribiliary plexus with the arterial supply of the caudate lobe is particularly interesting. By virtue of its bilateral arterial and portal supply, the caudate lobe probably represents an important bridge for collateral blood flow between the right and left livers. This anatomical information may in part explain why isolated ligation or embolization of right or left hepatic artery is usually fairly well tolerated in people with normal liver function²⁹. It may also explain why hepatic artery ligation is usually rather ineffective treatment for liver tumours³⁰.

The gastroduodenal artery, the dominant source of arterial supply to the common bile duct, is an important collateral supplier of the intrahepatic peribiliary plexus, and the liver as a whole. Because of this, occlusion of both the proper hepatic and gastroduodenal arteries may leave the liver, and particularly the IBDs, dangerously ischaemic. However, because of the collateral flow between right and left livers via the caudate lobe and peribiliary plexus, this may still be tolerated if there is a significant branch to the left liver from the left gastric artery.

These dissections also draw attention to the variable origins of the arterial supply of segment IV. Because of this the present authors recommend that, before harvesting a portion of liver from a living, related donor, it is particularly important to study carefully the intrahepatic arterial distribution angiographically to avoid unnecessary morbidity to the donor and provide an optimally prepared graft for the recipient. The same applies when performing liver resections involving segment IV. When preparing reduced liver grafts or splitting a liver in brain-dead organ donors, arteriography is inappropriate, and it is important to be aware that the artery to segment IV may arise from the right hepatic artery and to dissect the artery in the porta hepatis carefully to identify and preserve the artery to this segment^{31–34}. Alternatively, cadaver left liver grafts should be limited to segments II and III.

The close association of the peribiliary plexus with the arterial supply of the caudate lobe may also have important implications for the optimal preparation of reduced liver grafts. It suggests that it would generally be safer to remove the caudate lobe from either right or left liver grafts and cut the duct back fairly close to the parenchymal resection line. This is because it is unlikely that it will be established beforehand whether the caudate has a 'tree' or 'arcade' pattern of arterial supply or, if it

has a tree pattern, whether this arises from the right or left hepatic artery.

In the context of pancreatoduodenectomy or hepatic artery embolization for hepatic cancer, it is important to realize that loss of both hepatic artery and gastroduodenal artery (particularly if lesser collaterals have been damaged by mobilization of the liver) may result in extensive necrosis of the bile duct, with disastrous consequences³⁵. It is important, therefore, when doing pancreatoduodenectomy to identify carefully the proper hepatic, gastroduodenal and common hepatic arteries before dividing the gastroduodenal artery, and the bile duct. Particularly dangerous situations in this context are the right hepatic artery that arises from the superior mesenteric artery and when there is a low bifurcation into right and left hepatic arteries and the right hepatic artery ascends anteriorly to the common bile duct.

When doing high biliary-enteric anastomoses to repair iatrogenic common bile duct injuries or after resection of cholangiocarcinoma there is often pre-existing occlusion of significant arterial contributors to the peribiliary vascular plexus and it is fair to deduce from this study that the blood supply to the intrahepatic ducts to which one will be making the anastomosis will be coming from segmental branches of the right and left hepatic ducts. Therefore, in preparing for the anastomosis it behoves the surgeon to be very careful when dissecting around the porta hepatis and mobilizing the liver. Care must be taken not to ligate potentially useful collaterals such as a left hepatic artery arising from the left gastric artery, and great care must be taken to identify and not to damage any arteries in the porta hepatis.

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Short note

'Routine' pathological examination of the gallbladder is a futile exercise

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The authors, like most surgeons, routinely send gallbladders from all cholecystectomies for histological examination. In this paper, an attempt is made to determine whether this practice has any benefit.

Patients and methods

The computerized records of the pathology department at this hospital were used to categorize all gallbladders submitted for histopathological examination after cholecystectomy between January 1990 and January 1997. When a diagnosis of carcinoma of the gallbladder was made, the notes were examined to determine whether this was suspected before the histopathological diagnosis was known.

Results

A total of 1078 gallbladders was examined. There were 1045 with chronic and five with acute inflammation, five with cholesterosis, eight with xanthogranulomatous inflammation, three with dysplasia, six normals and six with adenocarcinoma (Table 1). Preoperative imaging was suggestive of cancer in two patients. In all cases, the surgeon commented that the gallbladder was suspicious at operation.

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Discussion

These findings suggest that routine histological examination of all gallbladders, regardless of operative findings, does not provide any additional useful information that benefits patients. Preoperative and peroperative suspicion were able to identify every case of carcinoma of the gallbladder in this series. Simple cholecystectomy is the treatment for all benign and premalignant gallbladder pathologies. More radical surgery for T₁ tumours (mucosa and muscle coat) has not been proven to improve survival¹⁻³. Thus any patient with early lesions not picked up by macroscopic examination will have received the appropriate treatment. Disease of stage II and above should be detectable macroscopically.

The value of examination of other surgical specimens such as appendices and skin lesions has been established by others^{4,5}. Prospective studies should be conducted to confirm the present findings, and also the true extent of workload reduction that can be achieved. The marginal cost is about £10 per specimen. If 30 per cent of specimens are deemed suspicious, then a saving of up to £1000 and 25 consultant-hours per year might be achieved in the authors' hospital. It is therefore suggested that the practice of routine histological examination of all removed gallbladders be abandoned, and a more considered approach adopted.

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Table 1 Details of patients with carcinoma of the gallbladder

Patient no.	Age (years)	Sex	Preoperative suspicion	Type of cholecystectomy	Operative findings	Type of tumour
1	80	F	Yes on ultra-sonography	Open	Grossly thickened gallbladder wall (?cancer)	Adenosquamous carcinoma
2	44	M	No	Open	Thickened gallbladder wall (?cancer)	Moderately differentiated adenocarcinoma
3	52	F	No	Laparoscopic, converted to open	Rock-hard gallbladder	Poorly differentiated adenocarcinoma
4	82	F	No	Open	?Cancer at level of porta/cystic duct	Well differentiated adenocarcinoma
5	60	F	No	Laparoscopic	Very thick-walled gallbladder (?cancer)	Moderately differentiated adenocarcinoma
6	57	F	Yes on ultra-sonography	Laparoscopic	Inflamed, indurated and oedematous gallbladder	Poorly differentiated adenocarcinoma

Comparison of POSSUM and the Portsmouth predictor equation for predicting death following vascular surgery

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Background The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scoring system has been proposed as an accurate predictor of death which takes account of case mix. It appears to overpredict death, and may have drawbacks which prevent accurate individual or subgroup analysis. An alternative system, the Portsmouth predictor equation for mortality (P-POSSUM) may have overcome these problems, but its apparent advantage could be related to inappropriate analysis of POSSUM predictions.

Methods Some 312 patients having arterial procedures were studied. POSSUM and P-POSSUM scores were used to predict death and compared with actual outcomes. The observed:predicted (O:E) mortality ratios were calculated by two methods for each of the scoring systems. First the analysis devised by the inventors of POSSUM was used and second the method devised for P-POSSUM.

Results The O:E ratio for POSSUM using its recommended 'exponential' method of analysis was 1.14, but it was 0.59 if the P-POSSUM 'linear' analysis was used. The O:E ratio for P-POSSUM using its correct method of analysis was 0.89, but it was 0.67 if the method of analysis devised for POSSUM was used.

Conclusion The O:E ratios for POSSUM and P-POSSUM were close to unity when the appropriate analysis was performed. Both POSSUM and P-POSSUM overpredicted death if the incorrect analysis was used.

The requirement for accurate audit of outcome in surgical practice has highlighted the problems of comparing crude mortality data from different units. The Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scoring system¹ was developed to overcome the problems of different case mix between units and has been shown to be a good predictor of morbidity and death in general, vascular and colorectal surgery^{2–4}. Recent reports have cited the tendency of POSSUM to overpredict death in fit patients undergoing minor surgery⁵ and in vascular⁶ and general surgical⁷ patients. In the context of comparative audit, a system which overpredicts mortality rate has the effect of making poor results look better than they actually are. In an effort to counteract the perceived shortcomings of conventional POSSUM, Whiteley *et al.*⁷ have devised a new version of POSSUM, still in the trial phase, called the Portsmouth predictor equation for mortality (P-POSSUM). P-POSSUM has been shown to reflect the observed mortality rate more closely than POSSUM in both general and vascular surgery^{6,7}. Although POSSUM and P-POSSUM are both derived from logistic regression analysis, analysis of the observed and predicted mortality rate is done in different ways, the methods of which have not been described explicitly in the respective publications.

Copeland and Prytherch have described the methods of analysis they recommend for POSSUM and P-POSSUM respectively in personal communications to one of the present authors (L.D.W.). The authors of the present study have no particular affiliation to either version of POSSUM. Therefore, this study is an independent

analysis using the methods described by the respective proponents of POSSUM and P-POSSUM. The authors' hypothesis is that perceived differences in the predictive accuracy of POSSUM and P-POSSUM may be explained by inappropriate analysis of the predicted deaths. The study compared the ability of POSSUM and P-POSSUM to predict the death of patients undergoing four categories of arterial surgery: carotid endarterectomy, abdominal aortic aneurysm repair, femoropopliteal bypass and femorotibial bypass; and analysed the effect of 'exponential' and 'linear' analyses on those predictions.

Patients and methods

The study was carried out in the vascular surgical unit of a university teaching hospital staffed by four consultant surgeons and their teams. Three hundred and twelve consecutive patients undergoing four categories of arterial surgery (carotid endarterectomy, abdominal aortic aneurysm repair, femoropopliteal bypass or femorotibial bypass) were recruited. Their median age was 72 (interquartile range 65–81) years and 212 (68 per cent) were men. Their POSSUM and P-POSSUM scores were calculated prospectively according to previously described criteria¹. The 30-day mortality rate was recorded by a combination of information from weekly vascular audit meetings, review of the notes, and hospital mortuary and general practitioner lists.

Linear analysis

Patients' predicted risk of death was calculated from POSSUM and P-POSSUM scores using the respective equations^{1,7}. Patients were divided into groups according to their predicted risk of death: less than 10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 and greater than 90 per cent. For each version of POSSUM, the number of patients falling into each mortality

group was multiplied by the average risk of death to give the predicted number of deaths in that group. The average risk in the 30–39 per cent group is 34.5 per cent, in the 40–49 per cent group 44.5 per cent, in the 50–59 per cent group 54.5 per cent and so on. This type of 'linear' analysis is that used by Whiteley *et al.*⁷ and allows each mortality band to be considered separately.

Exponential analysis

In the exponential method of analysis used by Copeland *et al.*¹, a cut-off risk of death is considered in each stage of the calculation. All patients whose predicted risk falls above the cut-off are grouped together. Therefore if the cut-off level being analysed is 80 per cent risk of death, the number of predicted deaths in this group is the result of the number of patients with 80 per cent or greater predicted risk of death, multiplied by 0.8. A difficulty arises if, as in the case of this study at the 40 per cent cut-off, the calculated number of predicted deaths above this cut-off falls below the number calculated for a higher cut-off. In this situation a second calculation should begin again from the lower cut-off. For the lowest cut-off (0 per cent), multiplication by zero is avoided by using the median predicted risk of the below 10 per cent mortality band, in this case 6 per cent.

Both the linear and exponential analyses were used for POSSUM and P-POSSUM predictions. The ratio of observed to predicted deaths (O:E ratio) was calculated for each analysis. An O:E ratio over 1.0 indicates that the scoring system underpredicts deaths, whereas a ratio less than 1.0 indicates overprediction of deaths.

Results

Three hundred and twelve operations were carried out on 312 patients as follows: 113 abdominal aortic aneurysm repairs (73 elective), 73 femoropopliteal bypasses, 67 femorotibial bypasses and 59 carotid endarterectomies. The total number of postoperative deaths was 41 (13 per cent); 25 after abdominal aortic aneurysm repair (four elective), ten after femorotibial bypass, five after femoropopliteal bypass and one following carotid endarterectomy. Thirty-eight deaths occurred before discharge and were all noted in the vascular audit and the hospital mortuary record. The three deaths after discharge occurred in a nursing home 17 days after elective aortic aneurysm repair, in the patient's home 21 days after femorotibial bypass, and during readmission to hospital for myocardial infarction 29 days after emergency aortic aneurysm repair.

Linear analysis

The results of 'linear' analysis applied to POSSUM and P-POSSUM are shown in *Tables 1* and *2* respectively. When this method was applied to predictions made by the conventional POSSUM, POSSUM appeared to overestimate the likelihood of death, the overall O:E ratio being 0.59. On the other hand, the mortality rate predicted by P-POSSUM appeared to agree well with observed rate, the overall O:E ratio being 0.89.

Exponential analysis

The results of 'exponential' analysis applied to POSSUM and P-POSSUM are shown in *Tables 3* and *4* respectively. When this method was applied to deaths predicted by POSSUM, POSSUM appeared to agree well with the

Table 1 'Linear' analysis of deaths predicted by POSSUM

Mortality group (%)	No. of patients	Actual no. of deaths	No. of deaths predicted by POSSUM*	Observed · predicted
<10	102	0	5	0.00
10–19	95	7	14	0.50
20–29	39	6	10	0.60
30–39	31	5	11	0.45
40–49	8	6	4	1.50
50–59	12	5	7	0.71
60–69	9	3	6	0.50
70–79	7	3	5	0.60
80–89	5	3	4	0.75
>90	4	3	4	0.75
0–100	312	70	70	0.59

*Rounded to the nearest whole number. POSSUM, Physiological and Operative Severity Score for enUmeration of Mortality and morbidity

Table 2 'Linear' analysis of deaths predicted by the Portsmouth predictor equation for mortality

Mortality group (%)	No. of patients	Actual no. of deaths	No. of deaths predicted by P-POSSUM*	Observed · predicted
<10	195	8	9	0.89
10–19	56	9	8	1.13
20–29	16	4	4	1.00
30–39	16	4	6	0.67
40–49	11	5	5	1.00
50–59	7	3	4	0.75
60–69	1	1	1	1.00
70–79	4	3	3	1.00
80–89	2	1	2	0.50
>90	4	3	4	0.75
0–100	312	41	46	0.89

*Rounded to the nearest whole number. P-POSSUM, Portsmouth predictor equation for mortality

Table 3 'Exponential' analysis of deaths predicted by POSSUM

Mortality group (%)	No. of patients	Actual no. of deaths	No. of deaths predicted by POSSUM*	Observed · predicted
0–49	275	24	17	1.35
10–49	173	24	17	1.35
20–49	78	17	16	1.00
30–49	39	11	12	0.92
40–49	8	6	3	2.00
.				
50–100	37	17	19	0.89
60–100	25	12	15	0.80
70–100	16	9	11	0.82
80–100	9	6	7	0.86
90–100	4	3	4	0.75
0–100	37 + 275 = 312	17 + 24 = 41	19 + 17 = 36	1.14

*Rounded to the nearest whole number. The dashed recalculation line separates two regions at which the predicted deaths for 40–100 per cent are fewer than those for 50–100 per cent so that the calculation has to begin again at 40–49 per cent (see methods).

Table 4 'Exponential' analysis of deaths predicted by the Portsmouth predictor equation for mortality

Mortality group (%)	No. of patients	Actual no of deaths	No. of deaths predicted by P-POSSUM*	Observed: predicted
0-29	267	21	43	0.49
10-29	72	13	7	1.86
20-29	16	4	3	1.33
...	...	...	...	...
30-69	35	13	11	1.18
40-69	19	9	8	1.13
50-69	8	4	4	1.00
60-69	1	1	1	1.00
...	...	...	...	...
70-100	10	7	7	1.00
80-100	6	4	5	0.80
90-100	4	3	4	0.75
0-100	10 + 35 + 72 + 16 = 312	7 + 13 + 21 = 41	7 + 11 + 7 + 3 + 4 = 61	0.67

*Rounded to the nearest whole number. The dashed recalculation line separates regions at which the predicted deaths for 60-100 per cent are fewer than those for 70-100 per cent so that the calculation has to begin again at 60-69 per cent; and at which the predicted deaths for 20-69 per cent are fewer than those for 30-69 per cent so that the calculation has to begin at 20-29 per cent (see methods).

Table 5 Observed:predicted mortality ratios for POSSUM and P-POSSUM calculated by the 'linear' and 'exponential' methods

	POSSUM O:E ratio		P-POSSUM O:E ratio	
	'Linear'	'Exponential'	'Linear'	'Exponential'
Abdominal aortic aneurysm	0.61	1.02	0.99	0.72
Femoropopliteal bypass	0.59	1.10	0.92	0.55
Femorotibial bypass	0.70	1.00	1.01	0.68
Carotid endarterectomy	0.66	1.05	0.95	0.71

The 'linear' and 'exponential' methods were devised for the P-POSSUM and POSSUM respectively O:E ratio, observed: predicted mortality ratio

observed mortality rate, the overall O:E ratio being 1.14. However, P-POSSUM overestimated the likelihood of death, the overall O:E ratio being 0.67.

The results of similar analyses applied to individual operations are summarized in *Table 5*.

Discussion

POSSUM is the best available system for assessing outcomes⁸ by risk-adjustment analysis. However, POSSUM has appeared inaccurate in predicting death when used by some surgeons. The results of this study support the view that both POSSUM and P-POSSUM are good predictors of death after arterial surgery if the correct analysis is used for each system. Using 'linear' analysis for

POSSUM or 'exponential' analysis to examine P-POSSUM yielded spurious results which made both systems overpredict the number of deaths.

The 'exponential' method was not described by the authors of POSSUM in their publications and its potential drawbacks have therefore not been open to critical review. Exponential analysis is unwieldy because it has to be stopped and restarted at a new level if the predicted number of deaths falls below that calculated at a higher cut-off. The point at which the recalculation has to be performed may vary between populations depending on their spread of predicted risk of death. It is unclear how subgroup analysis can be performed by 'exponential' analysis. For example, referring to *Table 3*, if one wanted to examine the O:E ratio for patients with a predicted risk of death of 30-59 per cent, the number of deaths in the 30-49 per cent and 50-59 per cent groups cannot simply be added because the groups are separated by a recalculation line and the 50-59 per cent band cannot be analysed independently of the 50-100 per cent band. A further difficulty with exponential analysis is its need to count and recount patients in the risk bands. A patient in the 90-100 per cent band is counted not only in this band but also in the 80-100 per cent, 70-100 per cent, 60-100 per cent and 50-100 per cent bands; whereas a patient with a risk of death of 55 per cent is only counted once, i.e. in the 50-100 per cent band. The prediction of death in individual patients may therefore be inaccurate. Notwithstanding these drawbacks, the present data show that POSSUM, when used with 'exponential' analysis, provides a reasonably accurate prediction of death in the whole population studied.

To those who wish to use POSSUM in their own units the simpler 'linear' analysis, which does not suffer the above drawbacks, would seem the obvious one to use. As the present results show, this would give the impression that POSSUM grossly overpredicted the risk of death.

POSSUM has been validated by units in the UK and abroad. P-POSSUM is still in a trial phase and needs further verification before it receives more widespread acceptance. P-POSSUM has the advantage that its analysis is more straightforward although there may be theoretical advantages in modelling terms of using exponential analysis⁹. Both POSSUM and P-POSSUM represent efforts to model clinical effects using mathematical equations. As such they are both constrained by the limitations of this method. For example, the lowest possible predicted risk of death using POSSUM is 1.08 per cent⁵ and that using P-POSSUM is 0.20 per cent. The POSSUM figure and possibly the P-POSSUM figure as well are higher than might be expected for a fit person undergoing a minor elective surgical procedure.

The data in this paper represent a unique cross-section of patients. The ultimate test of both POSSUM and P-POSSUM is how well their predictions fit clinical data from different units. It is perhaps surprising that these two systems, both derived from general surgical databases, fit a group of vascular surgical patients. If this goodness of fit can be reproduced in other vascular units POSSUM and P-POSSUM could be useful means to compare outcomes in different vascular units.

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Correlation of the anatomical distribution of venous reflux with clinical symptoms and venous haemodynamics in primary varicose veins

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Aim The aim of this study was to correlate the anatomical distribution of venous reflux with clinical symptoms and venous haemodynamics in patients with primary varicose veins.

Methods Venous reflux was examined using duplex colour Doppler ultrasonography in 266 legs in 191 patients. The venous refilling and reflux times were also measured.

Results Of the 266 legs, 82 per cent had reflux in the long saphenous vein (LSV), 26 per cent in the short saphenous vein (SSV), 62 per cent had incompetent perforators (IPs) in the calf and 48 per cent had reflux in the deep veins. LSV reflux combined with SSV reflux and/or IPs was associated significantly with severe venous disease and abnormal venous haemodynamics. Femoropopliteal reflux played a role in the development of venous eczema and ulcers when combined with superficial venous reflux.

Conclusion Patients at high risk of developing complications of venous disease may be identified by an accurate non-invasive evaluation of reflux patterns.

Primary varicose veins of the leg are bothersome, particularly when associated with complications such as lipodermatosclerosis and ulceration. Valvular incompetence of the superficial and perforating veins is considered the main pathological feature of primary varicose veins. Deep venous reflux of a primary non-thrombotic origin is also frequently present in the legs of patients with varicose veins^{1,2}. Because patients with varicose veins may have valvular incompetence in the superficial, perforating and deep venous systems alone, or in combination, it is difficult to determine which abnormality has the maximum bearing on the development of complications. With the application of duplex colour Doppler imaging, the incidence and anatomical distribution of venous reflux can be determined non-invasively in patients with varicose veins. This study correlated the pattern of reflux with clinical symptoms and venous haemodynamics.

Patients and methods

This study comprised a consecutive series of patients referred for the treatment of varicose veins. A detailed history and clinical examination were undertaken to exclude patients with secondary deep venous incompetence. Patients in whom post-thrombotic changes were later diagnosed by colour duplex imaging were excluded. Some 266 legs in 191 patients with primary varicose veins were studied. There were 43 men (61 legs) and 148 women (205 legs) ranging in age from 17 to 80 (mean 52.6) years. All symptomatic extremities had obvious varicose veins. According to the clinical classification for chronic venous insufficiency (CVI) by the International Consensus Committee on Chronic Venous Disease³, 192 limbs were assigned to class 2 (varicose veins), 14 to class 3 (oedema without skin changes), 54 to class 4 (pigmentation, venous eczema or lipodermatosclerosis) and six to class 6 (active venous ulceration).

A detailed examination of the entire venous system from the groin to the ankle was performed in all limbs using duplex colour

Doppler ultrasonography with 5- and 7.5-MHz probes (Quantum 2000; Siemens, Issaquah, Washington, USA). The superficial and deep venous systems were initially examined to exclude a post-thrombotic syndrome. All patients were examined on a standard tilt table in 30° reverse Trendelenburg, while placing weight mainly on the opposite limb. The long saphenous vein (LSV) from the saphenofemoral junction to the knee, and the superficial femoral vein distal to the termination of the deep femoral vein, were examined in the supine position. The short saphenous vein (SSV) from the saphenopopliteal junction to the calf, and the popliteal vein distal to the termination of the SSV, were assessed in the prone position. A 10-cm cuff was placed on the calf and an automatic cuff inflator (120 mmHg) was used for rapid inflation and deflation. Observations were recorded during cuff deflation and during sustained Valsalva manoeuvre. The duration of retrograde flow was measured from the onset of distal cuff deflation to the cessation of flow. Reflux was considered significant if the duration of retrograde flow exceeded 0.5 s. Incompetent perforators (IPs) were identified by squeezing the foot and calf. When flow was seen towards the superficial system, a perforating vein was considered incompetent. All scans were performed by the same experienced vascular technician.

Haemodynamic assessment of the venous reflux was made using photoplethysmography (Imexlab 9000, Imex Medical Systems, Golden, Colorado, USA). Photoplethysmography probes were secured to the skin 5 cm proximal to the medial malleolus. After five dorsiflexions of the ankle in a sitting position, the tracing was recorded until it returned to baseline. The procedure was repeated using a below-knee rubber tourniquet. The half venous refilling time ($VRT_{1/2}$) was calculated in seconds by measuring the refilling time necessary for the baseline shift to reach 50 per cent of the steady state after exercise. In this laboratory, a $VRT_{1/2}$ measurement greater than 7.3 s is considered normal⁴.

Almost all patients had a $VRT_{1/2}$ measurement using photoplethysmography before colour duplex scanning. Studies were separated by 1–7 days. Scans were interpreted at the time of examination by the technician and were reviewed by vascular surgery fellows. All interpreters were blinded to the results of the $VRT_{1/2}$ measurement.

Student's *t* test, the χ^2 test, analysis of variance and Fisher's protected least significant difference were used for statistical

analysis. Results are expressed as mean(s.d.). $P < 0.05$ was considered significant.

Results

Of the 266 limbs with primary varicose veins, 219 (82 per cent) had reflux in the LSV, 69 (26 per cent) had reflux in the SSV and 164 (62 per cent) had reflux in calf perforating veins (IPs). The overall incidence of superficial venous reflux was 95 per cent (253 of 266 limbs); in the remaining 13 limbs no venous reflux was found using duplex colour Doppler ultrasonography.

Superficial venous reflux was classified into eight patterns on the basis of the anatomical distribution of reflux combinations. LSV reflux and IPs (118 (44 per cent) of 266), and LSV reflux alone (56 (21 per cent) of 266), were the commonest patterns. Limbs with skin changes (CVI classes 4 and 6) were classified as having severe venous disease. Of the 60 legs with severe venous disease, LSV reflux was detected in 57 (95 per cent), SSV reflux in 19 (32 per cent) and IPs in 45 (75 per cent). Photoplethysmography revealed that the mean(s.d.) $VRT_{1/2}$ was significantly shorter in patients with severe venous disease than in those with CVI class 2 or 3 disease (4.0(1.8) s versus 5.9(2.1) s, $P < 0.0001$). This $VRT_{1/2}$ difference was eradicated by the application of a below-knee tourniquet (10.7(4.7) s versus 10.8(4.8) s).

The severity of venous disease and $VRT_{1/2}$ in relation to the distribution of superficial venous reflux is shown in Table 1. Severe venous disease was more common when LSV reflux was combined with SSV reflux and/or IPs ($P < 0.0001$). The $VRT_{1/2}$ was significantly shorter in legs with LSV reflux combined with SSV reflux and/or IPs, than in those with LSV reflux alone. From these clinical and haemodynamic observations, the 163 limbs with LSV reflux combined with SSV reflux and/or IPs were considered to be at higher risk for the development of complications from varicose veins (high-risk group). Legs with other patterns of reflux made up the low-risk group.

Of the 266 legs, 52 (20 per cent) had reflux in both the superficial femoral and popliteal veins (femoropopliteal reflux), 34 (13 per cent) had reflux confined to the superficial femoral vein (femoral reflux) and 41 (15 per cent) had reflux confined to the popliteal vein (popliteal reflux). The overall incidence of deep venous reflux was 48 per cent (127 of 266). The severity of venous disease and $VRT_{1/2}$ in relation to the distribution of deep venous reflux in the high- and low-risk groups is shown in Table 2. Femoropopliteal reflux was found more frequently in the high-risk group (43 (26 per cent) of 163) than in the low-risk group (nine (9 per cent) of 103) ($P < 0.001$). The incidence of severe venous disease was highest in legs with femoropopliteal reflux in the high-risk group, whereas no patient with femoropopliteal reflux in the low-risk group had skin changes. In the high-risk group, the $VRT_{1/2}$ was

Table 1 Severity of venous disease and half venous refilling time in relation to the distribution of superficial venous reflux

Pattern of venous reflux			CVI class ³				Incidence of CVI class 4 or 6 (%)	Mean(s.d.) $VRT_{1/2}$ (s)
LSV	SSV	IP	2	3	4	6		
No	No	No	11	1	1	0	7.7	7.5(1.9)
No	No	Yes	9	0	0	1	10.0	6.0(2.3)
No	Yes	No	15	1	0	0	0	6.6(2.0)
No	Yes	Yes	6	1	1	0	12.5	5.5(1.6)
Yes	No	No	47	3	6	0	10.8	5.8(2.0)
Yes	No	Yes	79	6	28	5	28.0*	5.1(2.1)*
Yes	Yes	No	9	0	8	0	47.1‡	5.0(2.8)
Yes	Yes	Yes	16	2	10	0	35.7†	4.5(2.1)†

LSV, long saphenous vein; SSV, short saphenous vein; IP, incompetent perforator; CVI, chronic venous insufficiency; $VRT_{1/2}$, half venous refilling time. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ versus group with reflux confined to the LSV (χ^2 test, analysis of variance, Fisher's protected least significant difference)

Table 2 Severity of venous disease and half venous refilling time in relation to the distribution of deep venous reflux in high- and low-risk groups

Deep venous reflux	CVI class ³				Incidence of CVI class 4 or 6 (%)	Mean(s.d.) $VRT_{1/2}$ (s)
	2	3	4	6		
High-risk group						
Femoropopliteal reflux	22	3	16	2	41.9*	3.8(2.0)†
Femoral reflux	9	1	6	0	37.5	4.4(1.5)*
Popliteal reflux	16	1	7	1	32.0	5.9(2.0)
No reflux	57	3	17	2	24.1	5.5(2.1)
Low-risk group						
Femoropopliteal reflux	9	0	0	0	0	5.2(1.8)
Femoral reflux	16	1	0	1	5.6	5.7(1.9)
Popliteal reflux	12	1	3	0	18.8	6.9(2.1)
No reflux	51	4	5	0	8.3	6.2(2.1)

CVI, chronic venous insufficiency; $VRT_{1/2}$, half venous refilling time. * $P < 0.05$, † $P < 0.0001$ versus no deep venous reflux (χ^2 test, analysis of variance, Fisher's protected least significant difference)

Table 3 Reflux time in legs with and without severe venous disease, and in high- and low-risk groups

	Superficial segment reflux time (s)	Deep segment reflux time (s)	Total limb reflux time (s)
Limbs with severe venous disease	7.6(4.4)	3.8(4.0)	11.2(7.1)
Limbs without severe venous disease	7.1(4.2)	2.9(4.4)	10.3(7.1)
High-risk group	8.3(4.0)	3.5(4.9)	12.3(7.5)
Low-risk group	5.5(4.0)*	2.5(3.5)	7.9(5.4)*

Values are mean(s.d.). * $P < 0.0001$ (low-risk versus high-risk group, Student's *t* test)

significantly shorter in legs with femoropopliteal reflux than in legs with no deep venous reflux. The mean(s.d.) VRT_{1/2} applied with a below-knee tourniquet was 8.5(4.7) s in legs with femoropopliteal reflux, 11.0(4.8) s in those with femoral reflux, 10.2(3.0) s in those with popliteal reflux and 11.8(4.6) s in those with no reflux. Although the VRT_{1/2} returned to normal after the application of a below-knee tourniquet in all groups, a significant difference remained between legs with femoropopliteal reflux and those with no reflux in the high-risk group ($P < 0.0001$).

The relationship between the severity of venous disease and reflux time measured with duplex colour Doppler ultrasonography is shown in Table 3. Superficial segment reflux time (Rts) was obtained by adding the reflux times of the LSV and SSV. Deep segment reflux time (Rtd) was obtained by adding the reflux times of the superficial femoral vein and the popliteal vein. Total leg reflux time (Rtt) was obtained by combining Rts and Rtd. In legs with severe venous disease, mean Rts, Rtd and Rtt did not differ significantly from that in legs without severe venous disease. Reflux times in legs in the high- and low-risk groups were compared. The high-risk group had significantly longer Rts and Rtt than the low-risk group.

Discussion

Conventional teaching is that CVI due to primary varicose veins is the result of incompetence of superficial and perforating veins, whereas the predominant cause of CVI due to post-thrombotic syndrome is deep venous reflux. However, many studies using descending venography or Doppler examination have found that deep venous reflux is not uncommon in patients with primary varicose veins^{1,2}. Recent studies in patients with CVI from primary varicose veins and post-thrombotic syndrome have identified the importance of reflux of the deep venous system including the femoral, popliteal and posterior tibial veins⁵⁻⁷. Others have reported that reflux of the superficial venous system is associated with severe venous complications⁸⁻¹². The variability of the relative contributions of reflux of the superficial, perforating and deep veins is probably related to the variability of chronic venous disease. From the clinical point of view, the majority of patients with primary varicose veins can be treated successfully by superficial venous surgery and elastic stockings. Patients with post-thrombotic changes have less good results. The short VRT in limbs with primary varicose veins measured by direct venous pressure

monitoring or photoplethysmography is usually corrected by the application of a below-knee tourniquet^{4,13}. When discussing the relative contribution of reflux to the development of severe venous disease, patients with primary varicose veins and post-thrombotic syndrome should be analysed separately to avoid confusion.

In this study, of 266 legs with primary varicose veins, LSV reflux was seen in 82 per cent, SSV reflux in 26 per cent, IPs in 62 per cent and deep venous reflux in 48 per cent. These results agree with those of other investigators who have reported that the incidence of LSV and SSV reflux, IPs and deep venous reflux is 43-60, 3-33, 50-57 and 20-41 per cent respectively^{9,14-16}. There is no doubt that multisystem incompetence exists in some legs with primary varicose veins. Because of this variability it is difficult to determine the relative contribution of each component to venous stasis. For practical purposes, it is reasonable to determine which types of reflux are associated with a higher risk for the development of venous complications. The present study showed that LSV reflux combined with SSV reflux and/or IPs was associated with severe venous disease. These clinical findings were supported by the haemodynamic assessment.

It is generally accepted that the VRT by photoplethysmography correlates closely with that measured by direct venous pressure monitoring^{13,17}. Recently, the reflux time measured by duplex ultrasonography has been reported to be useful for the evaluation of venous stasis. Welch *et al.*¹⁸ reported that a total valve closure time obtained by adding the valve closure time in the superficial femoral vein to that in the popliteal vein correlated significantly with the findings of descending venography. Weingarten *et al.*⁶ reported that the total limb deep segment reflux time was prolonged in ulcerated legs (mean(s.d.) 6.4(4.1) s) compared with that in legs without ulcers (5.2(3.2) s), although 11 per cent of the patients had a history of phlebitis⁶. In the present study the high-risk group had a significantly shorter VRT_{1/2} and significantly longer superficial and total reflux times than the low-risk group. Legs with severe venous disease, however, did not have significantly longer superficial, deep and total reflux times.

Femoropopliteal reflux plays an important role in the pathophysiology of venous stasis and affects venous haemodynamics in the presence of IPs and/or an SSV. In legs with deep venous reflux in the high-risk group, the VRT_{1/2} returned to normal with the application of a below-knee tourniquet. However, the VRT_{1/2} in legs with femoropopliteal reflux remained significantly shorter. A shortened VRT that does not normalize with the application of a below-knee tourniquet implies the presence of incompetence of the deep vein system, or perforators located distal to the tourniquet, or both. It is postulated that the high reflux volume through IPs may significantly shorten the VRT_{1/2} in the presence of femoropopliteal venous reflux. In contrast, the relatively small reflux volume in legs with femoral venous reflux or popliteal venous reflux does not influence venous stasis even in the presence of IPs. Gooley and Sumner¹⁹ reported that venous reflux is determined largely by saphenous and distal valvular function and that incompetence confined to the femoral vein has little effect. Hanrahan *et al.*²⁰ reported in 95 legs with venous stasis ulceration that 30 (32 per cent) had superficial, perforating and deep venous incompetence, 18 (19 per cent) had superficial and perforating venous incompetence, and 16 (17 per cent) had superficial venous

incompetence alone. In contrast, incompetence of the perforating or deep venous systems, or both, accounted for less than 10 per cent of venous stasis ulceration. These findings imply that superficial reflux is the predominant factor causing venous stasis in primary varicose veins, and that high reflux is prerequisite for severe venous disease. This result highlights the importance of superficial venous surgery to treat patients with venous ulceration due to primary varicose veins. Improvement of venous haemodynamics and healing of venous ulceration can be expected in the majority, irrespective of the coexistence of incompetent deep veins^{21,22}.

Multisystem and multilevel valvular incompetence contributes to venous stasis in legs with primary varicose veins, although reflux of the LSV is the most significant factor. LSV reflux combined with SSV reflux, IPs and femoropopliteal venous reflux is associated with severe venous disease. Accurate non-invasive evaluation using duplex colour Doppler ultrasonography helps to determine the best operative strategy.

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Management of acute leg ischaemia in the elderly

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Background Peripheral thrombolysis is advocated by some as the best initial treatment for acute leg ischaemia, but this may not be true for elderly patients. This study reviewed the management of acute leg ischaemia in patients aged over 75 years.

Methods Over a 5-year interval, 91 events of acute leg ischaemia in 84 patients were managed in a single district general hospital according to a local protocol. There were 60 women and 24 men of median age 81 (range 75–100) years. Fifteen patients were too elderly and infirm for active treatment and received anticoagulation alone. Some 76 events (84 per cent) occurred in patients suitable for active therapy: 33 were managed by initial surgery and 43 by peripheral thrombolysis with tissue plasminogen activator.

Results Overall outcome after 30 days was limb salvage in 48 (53 per cent), amputation in five (5 per cent) and death in 38 (42 per cent). In actively treated patients the corresponding values were 43 (57 per cent), four (5 per cent) and 29 (38 per cent). Initial successful revascularization was more likely following surgery (29 of 33 *versus* 25 of 43 events with thrombolysis, $P < 0.01$), but the 30-day outcome was similar in the actively treated groups owing to subsequent morbidity and mortality.

Conclusion A group of patients (mostly women) with emboli could be identified, using clinical criteria, who had a high chance of successful revascularization following embolectomy. Late outcome remained poor due to associated co-morbid conditions. Thrombolysis is associated with substantial risk in the elderly, and with high complication rates.

Results of treatment for acute leg ischaemia are variable^{1–4}. Amputation and mortality rates are high even in specialist vascular centres⁵. An integrated policy of surgery and peripheral thrombolysis produces optimal results in specialist units⁶. Many patients with acute leg ischaemia are elderly and this group has provided the greatest challenge to surgeons^{4,7}. Results of peripheral thrombolysis in the elderly have been reported to be inferior, with increased rates of complications and lower limb salvage⁸. Recent randomized studies have suggested that thrombolysis might be the best initial therapy for patients with acute leg ischaemia^{9,10}, but this may not be the case in the elderly. This study is a review of the management and outcome of patients over 75 years of age with acute leg ischaemia in Gloucester, UK.

Patients and methods

The aim was to review the management and outcome of all patients aged 75 years and over who were admitted to Gloucestershire Royal Hospital with acute leg ischaemia between 1 January 1991 and 31 December 1995. Acute leg ischaemia was defined as sudden deterioration in the circulation causing ischaemic pain at rest of less than 14 days' duration. Patients were identified using the computerized hospital patients administration system, which was searched for any diagnosis of leg ischaemia. Since 1992 all surgical patients have been entered on to a computerized audit system (AuditBase; Clinical Audit Systems, Ross, UK), which was used both to identify patients and to verify those detected through the hospital system. Case notes were reviewed and data collected on clinical details, method of treatment and outcome up to 30 days after admission. Additional data were available for patients who received peripheral

thrombolysis from the National Audit of Thrombolysis for Acute Limb Ischaemia database^{11,12}.

The principles of management of acute leg ischaemia were constant for the duration of the study and were established by local audit according to the following protocol. Patients with acute leg ischaemia of recent onset (less than 24 h), a source of emboli, no previous history of peripheral vascular disease and palpable pulses in the other leg were taken straight to the operating theatre for femoral embolectomy, usually under local anaesthesia. All other patients with acute critical ischaemia, including sensorimotor deficit and absent ankle Doppler ultrasound signals¹³ ('threatened viability' according to the Ad Hoc Committee on Reporting Standards¹⁴), received either urgent percutaneous or on-table angiography followed by accelerated thrombolysis¹⁵ or operation using standard vascular surgical techniques, including intraoperative thrombolysis¹⁶. Patients with subcritical ischaemia, no neurological deficit and audible ankle Doppler ultrasound signals¹³ ('viable' according to the Ad Hoc Committee¹⁴) were anticoagulated with heparin and underwent angiography when logistically convenient, followed by surgery or peripheral thrombolysis as appropriate.

Fifteen patients were considered too elderly or infirm for active therapy and received conservative treatment with anticoagulation alone. Five of these patients had a viable leg and the risks of intervention (apart from angioplasty) were judged too high. The remainder had critically ischaemic legs.

Decisions about active therapy using either surgery or thrombolysis in the remainder were made jointly following consultation between vascular surgeon and consultant radiologist. Techniques of thrombolysis used included low-dose intra-arterial infusion or high-dose bolus therapy with tissue plasminogen activator (tPA)¹⁵. Some patients were treated in a randomized trial comparing these two schedules; the conclusion was that both methods were similarly effective¹⁷. Outcome following lysis was analysed according to definitions proposed by the British Thrombolysis Study Group¹². Not included in this analysis were a few patients reviewed on elderly care wards with agonal thromboses in whom a joint decision was made with relatives not to intervene.

The study was conducted in a district general hospital of 400 beds with five admitting surgical units, two of which were led by consultant vascular surgeons. There was no formal emergency

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vascular rota, but advice was always available and was sought outwith office hours from one of the vascular specialists for difficult cases. Patients with subcritical ischaemia were transferred to one of the vascular teams the morning after emergency admission for further management. Some of the emergency embolectomies were performed by higher surgical trainees, but all complex vascular reconstructions were carried out by a consultant vascular surgeon.

Results

Ninety-one events of acute leg ischaemia were identified in 84 patients during the study. The median age was 81 (range 75–100) years. There were 60 women and 24 men. Seventy-six events (84 per cent) occurred in native vessels and 15 (16 per cent) involved a graft thrombosis. Some 33 events (41 per cent) resulted in ischaemic pain alone ('viable') and 47 (59 per cent) included a sensorimotor deficit ('threatened'), including two instances of distal skin necrosis. In the remainder, severity of ischaemia was not recorded.

Conservative treatment

According to protocol, 15 events were treated conservatively with anticoagulation alone, 33 involved urgent surgery (thromboembolectomy or bypass) and 43 involved initial angiography followed by intra-arterial thrombolysis (Table 1). On the 15 occasions (16 per cent) when a decision was made to use conservative treatment with anticoagulation and analgesia, this was generally for the oldest (median 86 years) and most infirm patients, often with advanced ischaemia. One patient benefited from iliac angioplasty for inflow disease and one improved after chemical sympathectomy. Three other patients with 'viable' limbs improved sufficiently after anticoagulation to be discharged without further therapy; one required amputation. The mortality rate (nine of 15 patients) was highest in this group (Table 2).

Surgical treatment

Some 76 events (84 per cent) occurred in a patient fit enough to have active treatment by either surgery or thrombolysis. Thirty-three events in 33 patients were initially managed surgically. Thirty-one patients had an embolectomy and two a surgical bypass (one femoro-

Table 2 Outcome of treatment at 30 days

	Conservative (anticoagulation)	Surgery	Thrombolysis	Total
No. of episodes of 15 treatment	33	43		91
Relief of ischaemia	—	29	25	54 (59)
Limb salvage	5	22	21	48 (53)
Amputation	1	1	3	5 (5)
Death	9	10	19	38 (42)

Values in parentheses are percentages

peroneal and one axillobifemoral). The ischaemia was successfully relieved by operation in 29 patients. Of the four with unrelieved ischaemia, two had major amputations (one of whom died) and the others died without a further procedure (Table 3). This group contained a high number of patients with 'threatened' limbs (21 of 33), with the shortest duration of ischaemia and all occlusions were in native vessels.

Peripheral thrombolysis

Forty-three events in 37 patients were managed initially by diagnostic angiography followed by intra-arterial thrombolysis. This group had the largest proportion of patients with 'viable' limbs (19 of 43) and included all but two of a total of 13 graft thromboses in the study. Six patients were treated on multiple occasions (maximum three times); five had recurrent prosthetic graft occlusions. tPA was used in 37 events (high-dose bolus, 23; low dose, 14), and low-dose streptokinase in six. These latter patients were managed in the earliest part of the series. Complete or partial lysis was recorded for 25 of the 43 events, with relief of ischaemia significantly lower than that after initial surgery (29 of 33 patients, $P < 0.01$, χ^2 test). Eight patients had angioplasty during, or after, successful lysis when a residual stenosis was identified. In the absence of an underlying cause for thrombosis, patients were treated subsequently with oral anticoagulation. Lysis failed to restore the circulation in 18 of 43 cases: eight patients died without further intervention, three required amputation (one died), two required

Table 1 Patient data and treatment

	Conservative (anticoagulation)	Surgery	Thrombolysis
No. of episodes of treatment	15	33	43
Median (range) age (years)	86 (75–100)	82 (75–98)	81 (75–91)
Median (range) duration of ischaemia	30 h (2 h to 14 days)	12 h (2.5 h to 14 days)	72 h (3 h to 14 days)
Sex ratio (M:F)	3:12	5:28	20:23
No. of grafts	2	0	13
Sensorimotor deficit ('threatened')	9	21	17
No sensorimotor deficit ('viable')	4	10	19
Status unknown	2	2	7

Table 3 Causes of death

	Conservative (anticoagulation)	Surgery	Thrombolysis
No. of patients	9	10	19
Multiorgan failure	3	1	4
Unrelieved ischaemia	1	3	1
Renal failure		2	2
Embolization of other arteries	1	1	2
Bleeding gastric ulcer		1	
Malignant disease or aneurysm	3	1	1
Stroke	1	1	
Major haemorrhage			2
Pneumonia			1
Myocardial infarction			2
Cardiac failure			2
Pulmonary embolism			1
Septicaemia			1

embolectomy (one died), one had a jump graft but died subsequently, one obtained limb salvage after femorotibial bypass, and three survived with an intact limb without further intervention. For comparison, during the interval of the study there were 62 episodes of thrombolysis for acute leg ischaemia in 49 patients under 75 years of age.

Complications and outcome

Outcome at 30 days is detailed in Table 2. Overall outcome was limb salvage in 48 (53 per cent), amputation in five (5 per cent) and death in 38 (42 per cent). There were no specific recorded complications following conservative therapy with anticoagulation, although mortality was highest in this group (nine of 15 patients). Recorded complications after surgery (three major, two minor) included two strokes (one fatal), fatal renal failure, compartment syndrome which did not require fasciotomy, and a wound infection. Complications were more frequent after thrombolysis; the ten major complications included haemorrhage in four (groin haematoma requiring surgery, two; fatal retroperitoneal haemorrhage, one; haematuria, one), fatal renal failure in two, fatal myocardial infarction in two, one fatal septicaemia and one distal catheter perforation during lysis. Minor complications also occurred in four patients, comprising two groin haematomas and two dislodgements of the infusion catheter. The principal causes of death in all groups, established from clinical information and autopsy data when available, are shown in Table 3.

Discussion

Patients with simple emboli and normal peripheral arteries who were previously treated successfully by embolectomy have become a rarity. The majority of today's patients with acute ischaemia have acute on chronic thrombosis, a condition for which the Fogarty catheter produces less certain results¹⁸. Even those with emboli now frequently have coexisting peripheral arterial disease. For these reasons, intra-arterial catheter thrombolysis may seem an attractive alternative to operation for acute leg ischaemia⁶. New agents, such as tPA and recombinant urokinase, together with modern techniques of accelerated thrombolysis, now allow most acutely ischaemic legs to be managed without surgery¹⁹.

Randomized trials comparing surgery and thrombolysis are rare, and are difficult to perform and interpret because of the wide variation in patients and their presentation. Most of the 393 patients in the Surgery *versus* Thrombolysis for Ischaemia of the Lower Extremity (STILE) study⁹ had chronic ischaemia, but analysis of the subgroup who had symptoms for fewer than 14 days revealed that these patients had a lower amputation rate and shorter hospital stay. In another study, patients randomized to initial surgery had a high perioperative mortality rate due to cardiorespiratory complications; this led to a significant survival advantage in those treated initially with thrombolysis¹⁰. Initial results of the Thrombolysis Or Peripheral Arterial Surgery (TOPAS) study were aimed primarily at selecting the optimal dose of urokinase for an ongoing comparison with surgery²⁰. Even if later results are encouraging, it is unlikely that an empirical policy of initial treatment with thrombolysis will suit all patients with acute leg ischaemia or be available in all vascular units.

The present study suffers from all the usual problems associated with a retrospective review, and conclusions must be guarded. However, randomized trials often exclude the elderly and are never likely to be completed in this patient group. The first significant finding was that the majority of elderly patients with acute leg ischaemia were women, a significant reversal from the usual male predominance in vascular disease⁷. This female preponderance was greatest in the group selected on clinical grounds as likely to have emboli suitable for immediate embolectomy. In this group embolectomy was a highly efficient means of restoring blood flow. Despite the high initial success rate in 29 of 33 cases, ten patients died giving a mortality rate similar to that of 32 per cent reported in a previous study⁷.

The overall results of treatment in the elderly are poorer than those for younger patients¹⁻⁴. One reason is the high proportion of elderly patients unsuitable for active treatment (16 per cent in this study). Such patients often remain unmentioned in clinical reports. They include those with agonal thrombosis, and improving outcome in this group would be possible only by improving the general medical condition of the patient, a factor that plays an unusually high part in the outcome in acute leg ischaemia²¹.

In this study the results of initial treatment with thrombolysis were inferior to those of surgery. Ischaemia was relieved (complete or partial lysis) significantly less often than after embolectomy (25 of 43 events *versus* 29 of 33), although the overall outcome was not significantly different between the groups. Complications from thrombolysis were common and sometimes fatal. In particular, haemorrhage was the cause of death in two patients, both of whom had retroperitoneal haematoma requiring operation.

Peripheral thrombolysis is a successful treatment modality in the management of leg ischaemia, and in many centres it is used routinely⁶. Nowadays, in most patients with acute ischaemia, major vascular reconstruction is the alternative, not embolectomy. Such surgery is associated with significant morbidity in an elderly high-risk population⁸. However, it must be remembered that thrombolysis is often only an initial treatment for acute leg ischaemia, as many patients will require angioplasty or reconstruction to deal with an underlying stenosis (the cause of the occlusion). Nevertheless, lysis may reduce the magnitude of any necessary surgery. It is the perioperative complications of surgery that may be the most significant influence on outcome¹⁰. It is often stated that surgery can be postponed until after an attempt at limb salvage with thrombolysis, but in this study few patients in whom thrombolysis failed were fit or suitable for subsequent operation.

It is not possible to make sweeping statements about the superiority of surgery for acute leg ischaemia in the elderly from this retrospective study; however, there is clearly a question regarding whether elderly patients should be treated differently from younger patients with the condition. A group of elderly women with emboli can be identified, using simple clinical criteria, in whom relief of ischaemia is frequently possible using a Fogarty catheter⁷. However, elderly patients with acute leg ischaemia represent a very high-risk group, even following successful revascularization. In the present study the results of initial treatment with peripheral thrombolysis were not good, but most of the patients initially treated with lysis were not suitable for balloon catheter extraction

of thrombus and it is possible that the results of emergency vascular reconstruction would have been as poor. A cautious, informed approach must be taken before embarking on primary thrombolysis in elderly patients; the best results are likely to be obtained by experienced vascular surgeons and radiologists working together, using an integrated policy of surgery and thrombolysis, and paying close regard to the general medical condition of the patient.

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Reduced total antioxidant capacity predicts ischaemia–reperfusion injury after femorodistal bypass

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Background Antioxidant defence systems are essential to protect the body from harmful free radicals released following ischaemia–reperfusion. The aim of this study was to examine the total antioxidant capacity (TAC) of patients with chronic critical leg ischaemia undergoing femorodistal bypass and to correlate this with lipid peroxidation, changes in capillary permeability and clinical outcome.

Methods Twenty-five patients, 15 men and ten women of median age 71 (range 62–79) years, and 15 matched controls were studied. Blood was taken before operation and after reperfusion, with assays performed for malondialdehyde (a product of lipid peroxidation) and total antioxidant capacity. Changes in capillary permeability were measured by changes in the urinary albumin:creatinine ratio (ACR) following reperfusion of the ischaemic leg and expressed as a percentage increase from the preoperative value. Clinical outcome in terms of the systemic inflammatory response syndrome (SIRS) was recorded.

Results Vascular patients who developed clinical evidence of a systemic inflammatory reaction following revascularization had a significantly reduced TAC compared with the controls (490 versus 860 $\mu\text{mol/l}$; $P < 0.01$, Mann–Whitney U test). These patients also demonstrated an increase in lipid peroxidation (0.5 versus 0.25 $\mu\text{mol/l}$, $P < 0.05$) and vascular permeability, as measured by the percentage increase in ACR (365 versus 130 per cent, $P < 0.01$).

Conclusion Vascular patients with a lower TAC developed increased capillary permeability as a result of ischaemia–reperfusion, which progressed to SIRS. TAC may provide a test to identify 'at risk' patients. It may be possible to augment their defence with exogenous antioxidants.

The human body is continuously exposed to potentially harmful oxidative stresses. These may arise from exogenous sources such as diet and environmental pollution¹. Alternatively, many oxidants are generated endogenously during normal physiological processes. These include products of mitochondrial respiration as well as oxidants generated by phagocytic cells of the immune system². Amongst the important oxidant species, particular attention has focused on free radicals. Free radicals are usually unstable and highly reactive, being capable of abstracting electrons from (oxidizing) surrounding molecules. In this way vital biological structures such as DNA, proteins and lipids can be damaged and cellular functions disrupted³.

To withstand the constant oxidative stresses, the body is endowed with a number of antioxidant systems (Table 1). The concentration of various antioxidants varies widely between individuals, being a function of their diet (ascorbate, α -tocopherol), synthetic function (proteins) and metabolic breakdown pathways (uric acid, bilirubin)⁴. Furthermore, the momentary levels of the chain-breaking antioxidants depend not only on their intake and production, but also on their consumption or the ongoing levels of oxidative stress. Thus, antioxidant status is a measure of increasing importance as the understanding of the process of oxidative damage increases.

At least 75 per cent of patients with chronic critical leg ischaemia are smokers⁵. Antioxidants are especially

important in smokers, as each puff of a cigarette is estimated to contain 10^{14} free radicals in the tar phase and 10^{15} in the gas phase⁶. Smokers, not surprisingly, have a lower antioxidant capacity than non-smokers⁷. Ongoing critical leg ischaemia may also deplete antioxidant capacity. In patients undergoing revascularization for leg ischaemia, the generation of toxic free radicals plays an important role in the pathophysiology of ischaemia–reperfusion. This may put patients at risk of developing the potentially fatal complications of non-cardiogenic pulmonary oedema and renal failure^{3,8}.

While it is possible to measure all the chain-breaking antioxidants individually, this is both time consuming and expensive. In addition, there seems to be cooperation

Table 1 Antioxidant systems of the body

Enzymes	Intracellular
	Superoxide dismutase Catalase Glutathione peroxidase–glutathione
Chain-breaking antioxidants	Extracellular
	Ascorbic acid Urate Sulphydryl groups Bilirubin
Preventive antioxidants	Membranes
	Tocopherols (vitamin E) Carotenoids
	Transferrin, caeruloplasmin, haptoglobin, haemopexin

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between various antioxidants during oxidative stress; looking at one in isolation may not reflect their combined action. A variety of new techniques has been developed to measure total antioxidant activity in biological fluids; the authors have used an enhanced chemiluminescent assay for total plasma antioxidant capacity which has been used to demonstrate changes in antioxidant capacity during aortic aneurysm surgery^{9,10}. The most damaging effect of free radicals is lipid peroxidation, a complex phenomenon which results in structural and functional cell damage¹¹. One of the relatively stable end products of lipid peroxidation is malondialdehyde (MDA), which was measured as a marker of lipid peroxidation in this study¹¹. Cell membranes are composed of polyunsaturated fatty acid and phospholipid, and are subjected to the effects of lipid peroxidation, which results in a generalized increase in endothelial permeability manifested by micro-albuminuria¹².

Patients and methods

The protocol used in this study was approved by the local ethics committee.

Twenty-five non-diabetic patients, 15 men and ten women of median age 71 (range 62–79) years, undergoing elective femoro-distal bypass surgery for chronic critical leg ischaemia were studied prospectively¹³. The patients had a similar duration of tissue ischaemia; two had tissue necrosis, but none had an infected ulcer. Fifteen matched controls were also studied, consisting of patients who had been attending the orthopaedic outpatient clinic for at least 1 year after surgery and who considered themselves mobile (Table 2)

Peripheral venous blood samples were taken from patients before operation, after cross-clamping the femoral artery and 5 min after release of the clamps. The anastomoses were performed simultaneously, with all clamps being released within seconds of one another. Further samples were taken 1, 4, 12 and 24 h after operation. The blood was collected in sterile bottles containing ethylenediamine tetra-acetic acid as an anticoagulant and immediately centrifuged with plasma, frozen and stored at -70°C for subsequent analysis. Urine was collected before operation and every hour after induction of anaesthesia. Urine was also frozen for subsequent analysis of albumin concentration. Blood and urine specimens were also taken from the control population. The patient's postoperative course was followed until discharge and the incidence of sepsis or systemic inflammatory response syndrome (SIRS), as defined by the American College of Chest Physicians–Society of Critical Care Medicine, was recorded (Table 3)¹⁴.

The anaesthetic agents and epidural analgesia used were standard in all cases. The median cross-clamp time was 48 (inter-quartile range (i.q.r.) 40–57) min and the length of operation was 210 (i.q.r. 150–240) min.

Total antioxidant capacity of plasma

The enhanced chemiluminescent assay for total antioxidant activity in body fluids has been described elsewhere⁹. The assay uses the enzyme horseradish peroxidase to catalyse the reaction between a hydrogen acceptor (oxidant) such as perborate and a hydrogen donor such as the chemiluminescent substrate luminol. When oxidized, luminol emits light, the kinetics of which can be influenced favourably by the addition of an enhancer such as *para*-iodophenol, which produces a constant source of free radical intermediates and stable and prolonged light emission. The light emission is sensitive to interference by antioxidants and the duration of suppression is proportional to the concentration of antioxidants. The duration of suppression caused by the specimens is compared with that of a standard solution of the water-soluble α -tocopherol analogue trolox, and the antioxidant

Table 2 Demographic details

	Patients (n = 25)	Controls (n = 15)
Sex ratio (M:F)	15:10	9:6
Median (range) age (years)	71 (62–79)	68 (56–82)
Smokers	21 (1.5 packs daily for 55 years)*	11 (1 pack daily for 52 years)*
Ischaemic heart disease	16	9
Median (range) ankle:brachial pressure index	0.2 (0–0.3)	0.9 (0.8–1.1)

*Values are medians

Table 3 Definition of systemic inflammatory response syndrome and sepsis¹⁷

SIRS	Signs of a systemic response (two of the following). Fever or hypothermia (core or rectal temperature greater than 38.4°C or less than 35.6°C) Tachycardia (heart rate greater than 90 beats per min) Tachypnoea (respiration greater than 20 breaths per min (if patient is mechanically ventilated, greater than 10 l/min)) White blood cell count greater than $12 \times 10^9/\text{l}$ or less than $4 \times 10^9/\text{l}$, or the presence of more than 0.1 per cent immature neutrophils
Sepsis	The presence of SIRS associated with a confirmed infectious process

SIRS, systemic inflammatory response syndrome

levels in the specimens are calculated as micromoles of trolox equivalent per litre.

Malondialdehyde production

Measurement of MDA provides a convenient index of lipid peroxidation¹⁵. The classical determination of MDA by the thiobarbituric acid method is influenced by much interference and its reproducibility is not satisfactory¹⁶. We used the LPO-586 method (Bioxystech, Cedex, France) This method uses a chromogenic reagent which reacts with MDA at 45°C . Condensation of one molecule of MDA with two molecules of the chromogenic reagent yields a stable chromophore with maximal absorbance at 586 nm. Some 200 μl of plasma was added to 650 μl of the chromogenic reagent and the reaction was started by the addition of 150 μl of 37 per cent aqueous hydrochloric acid. The test tube was mixed, incubated for 60 min in a 45°C water bath and then cooled in ice. The absorbance at the 586-nm wavelength was then measured in a spectrophotometer. Control values were obtained by replacing plasma with water. A standard curve was prepared from serial dilutions of 1,1,3,3-tetra-methoxypropane 100 $\mu\text{mol/l}$ in Tris–hydrochloric acid buffer 20 mmol/l at pH 7.4. Reproducibility was determined by assays done over 10 days under the same experimental conditions. The within-assay variation was 1.8 per cent and the between-assay variation of 12 samples measured on five separate occasions was 3.0 per cent.

Albumin excretion

Urinary microalbumin concentration was measured using radioimmunoassay (Diagnostic Products, Wallingford, UK). The intra-assay coefficient of variance of this technique was 3.5 per cent at 9.4 mg/l with a limit of detection of 0.9 mg/l. Albumin excretion was expressed as the albumin:creatinine ratio (ACR)

to compensate for changes in urinary flow during the investigation (normal upper limit of ACR was 1.0).

Statistical analysis

Results are expressed as median and interquartile range. Univariate analysis for all variables was performed to determine the distribution of the variables, and the Mann-Whitney *U* test was used as the test of significance. Wilcoxon's signed rank test was used for paired data.

Results

Patients and controls were well matched for age and reported smoking habit (Table 2). All patients undergoing bypass surgery had an ankle systolic pressure of less than 50 mmHg and orthopaedic controls had an ankle:brachial pressure index greater than or equal to 1.0. The incidence of the SIRS was 40 per cent (ten of 25 patients). There was no difference in disease severity between those who developed SIRS and those who did not; all patients in both groups suffered rest pain of similar duration, and one patient in each group had tissue necrosis. The smoking history was similar for both groups. The grafts consisted of seven femoroposterior tibial, six femoro-anterior tibial, six femoroperoneal, three femorolateral plantar and three femorodorsalis pedis grafts, distributed equally between the SIRS and non-SIRS groups. The types of graft used were also similar. The SIRS group consisted of five *in situ* vein grafts, three polytetrafluoroethylene (PTFE) with Miller vein cuff and two composite grafts of PTFE and vein. The non-SIRS group contained nine *in situ* vein grafts, four PTFE with Miller vein cuff and two composite grafts. There were no graft occlusions or amputations during the 7-day study interval.

Antioxidant capacity

The total antioxidant capacity (TAC) of patients undergoing limb revascularization was significantly lower than in controls (765 versus 1130 $\mu\text{mol/l}$; $P < 0.05$, Mann-Whitney *U* test). However, the patients who developed a systemic inflammatory reaction to the surgery had a lower preoperative antioxidant capacity than those who had an uneventful postoperative recovery (490 versus 860 $\mu\text{mol/l}$, $P < 0.01$). This continued during surgery; patients who developed SIRS had a greater reduction in plasma TAC after reperfusion (230 versus 640 $\mu\text{mol/l}$ at 1 h after reperfusion; $P < 0.05$, Mann-Whitney *U* test) (Fig. 1).

Malondialdehyde

MDA concentration, used as a marker of lipid peroxidation and hence of free radical damage, was significantly greater in the vascular patients before operation compared with that in controls (0.67 versus 0.25 $\mu\text{mol/l}$; $P < 0.05$, Mann-Whitney *U* test). Patients who subsequently developed SIRS had a higher preoperative level of MDA (1.4 versus 0.5 $\mu\text{mol/l}$, $P < 0.01$) (Fig. 2). During the course of surgery there was no significant change in MDA concentration in patients whose recovery was uncomplicated. By contrast, those who developed SIRS demonstrated a significant increase following reperfusion which was maximal at 1 h (1.4 versus 1.8 $\mu\text{mol/l}$; $P < 0.05$, Wilcoxon signed rank test).

Spearman's rank correlation test demonstrated a negative correlation between preoperative antioxidant capacity and MDA concentration (Fig. 3).

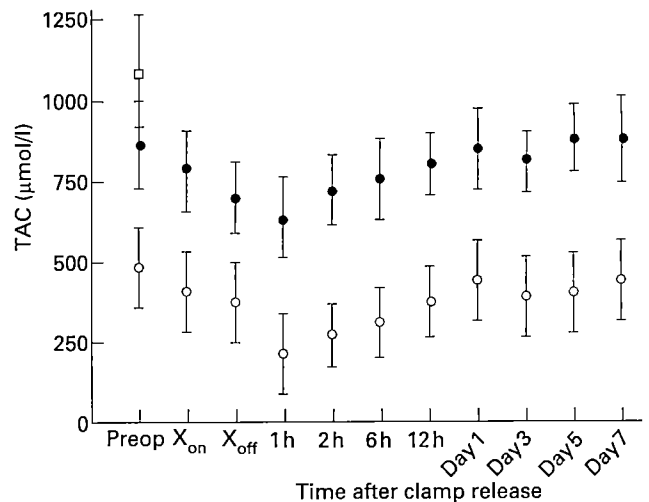


Fig. 1 Changes in plasma total antioxidant capacity (TAC) in controls (□), patients who did not develop systemic inflammatory response syndrome (SIRS) (●) and those who developed SIRS (○) following revascularization. Values are median (interquartile range). X_{on} , cross-clamp on; X_{off} , sample taken within 5 min of cross-clamp release

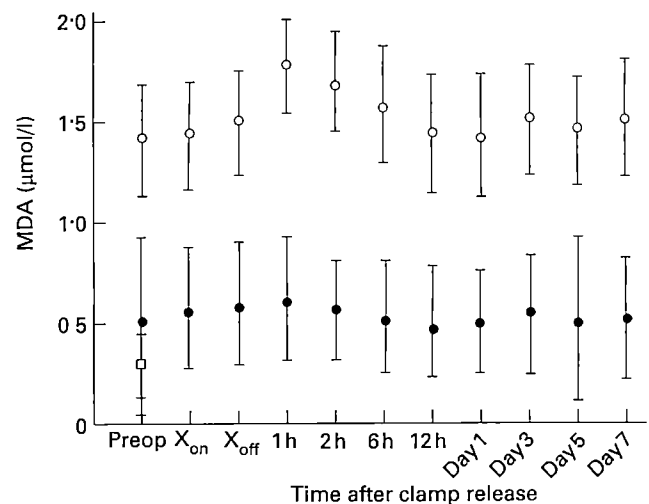


Fig. 2 Malondialdehyde (MDA) levels in controls (□) and patients who developed (○) or did not develop (●) systemic inflammatory response syndrome. Also shown are the changes in MDA concentration following revascularization. Values are median (interquartile range). X_{on} , cross-clamp on; X_{off} , sample taken within 5 min of cross-clamp release

Albumin:creatinine ratio

Changes in vascular permeability were determined by measurement of renal albumin excretion. The ACR was significantly greater before operation in the vascular patients than in controls (5.3 versus 1.0, $P < 0.01$). There was no difference before operation between patients who developed complications following surgery and those who did not. However, the group that developed SIRS had a significantly greater increase in ACR (365 versus 130 per cent 1 h after reperfusion of the ischaemic limb, $P < 0.01$) (Fig. 4).

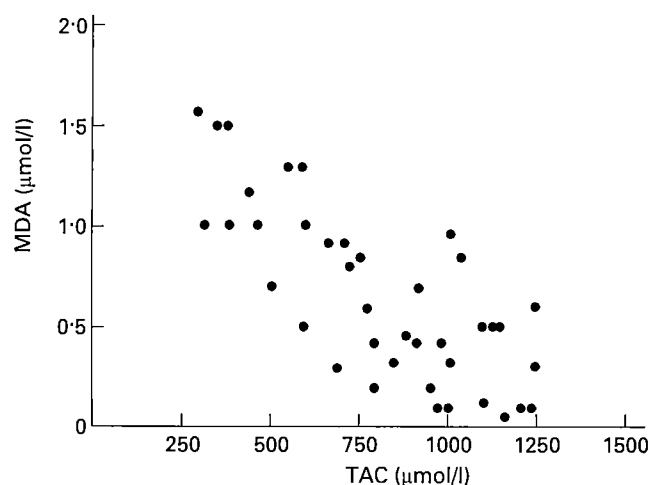


Fig. 3 Spearman's rank correlation test between preoperative total antioxidant capacity (TAC) and malondialdehyde (MDA) concentration ($r_s = -0.69$, $P < 0.01$)

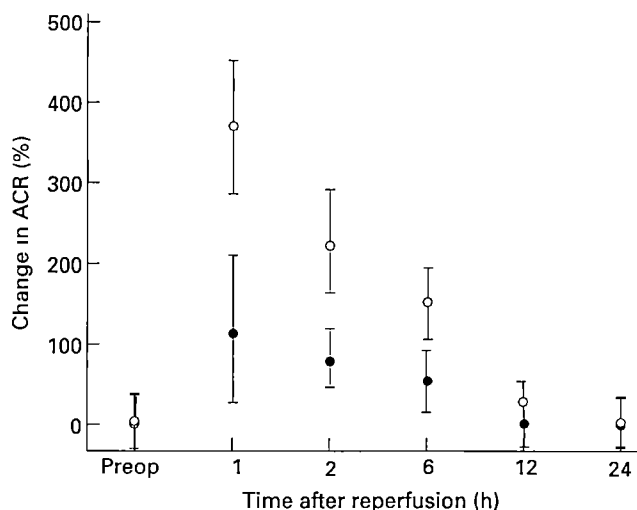


Fig. 4 Changes in renal albumin : creatinine ratio (ACR) following revascularization in the group with systemic inflammatory response syndrome (SIRS) (○) and the group without SIRS (●). Values are median (interquartile range)

Discussion

Free radical activity and oxidative damage has been implicated in the pathogenesis of a number of diseases. In particular, their role in the development of atherosclerosis has received much attention¹⁷⁻¹⁹. Antioxidants provide the first line of defence against free radicals. Any measurement of antioxidant status can be interpreted only in the light of the antioxidants it detects. The chemiluminescent assay does not assess the ability of plasma to remove potentially dangerous transition metal ions (i.e. preventive antioxidant status), nor can it simulate oxidative stress within biological membranes. It does, however, provide a simple and reproducible method of assessing free radical scavenging (chain-breaking) antioxidants in solution⁹. Previous studies have examined individual antioxidants in patients with peripheral vascular disease and found lower levels of these elements in patients than in controls^{20,21},

although no difference in plasma TAC was found between controls and claudicants²². In chronic critical ischaemia, the TAC of the plasma was reduced and the vascular patients also had evidence of free radical damage, as measured by lipid peroxidation, and an increase in vascular permeability. There was also a negative correlation between the preoperative plasma TAC and MDA concentration.

The term SIRS was developed to imply a clinical response arising from a non-specific insult¹⁴. SIRS results in prolonged postoperative hospital stay and may develop into severe sepsis and septic shock²³. Of patients who develop SIRS, 11 per cent progress to adult respiratory distress syndrome, 42 per cent to disseminated intravascular coagulation and 41 per cent to acute renal failure²³. Identification of patients at risk of SIRS may help to prevent such problems.

Patients who developed SIRS following surgery had lower preoperative plasma TAC than those who had an uncomplicated postoperative course. There was no difference in risk factors or smoking history between the groups. No correlation between preoperative antioxidant levels and postoperative complications was seen in a study of patients undergoing abdominal aortic surgery¹⁰. However, these patients were not assessed for the development of SIRS after operation. The study also failed to show a correlation between plasma TAC and smoking, which has been described previously⁷. In the present study patients who developed SIRS had the greatest increase in the concentration of MDA, a marker of free radical damage, following reperfusion.

The changes in plasma TAC were also reflected by the increased renal excretion of albumin. The degree of microalbuminuria is related to the severity of the surgery and appears to have prognostic implications²⁴. This was confirmed in the present study, as the patients who developed SIRS had a greater increase in ACR following reperfusion. There was no significant difference in the preoperative ACR between the two groups. Patients may be able to withstand considerable oxidative stress with only a small increase in vascular permeability.

It would appear that some patients have a lower plasma TAC regardless of the duration of ischaemia, smoking habit and other known risk factors. This may be due to diet, or to an endogenous defect in protein production or metabolic pathways and may help to explain why only some patients have benefited in the trials of various antioxidant supplements²⁵.

Plasma TAC may provide a measurement to identify patients at risk of postoperative complications. Discovering a method to improve TAC could help reduce the risk of complications associated with reperfusion injury.

Acknowledgements

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Laparoscopic stoma formation for faecal diversion

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Background Laparoscopic creation of an intestinal stoma may be preferable to open operation when intervention is required solely for faecal diversion.

Methods Experience with laparoscopic intestinal stoma formation for faecal diversion from a single institution is presented.

Results A total of 55 stomas were studied, 40 laparoscopic and 15 open. The conversion rate from laparoscopic to open operation was 5 per cent. Mean(s.e.m.) operating time was significantly reduced for laparoscopic stomas (54(4.7) versus 72(8.7) min). Time to return of bowel function was significantly reduced (1.6(0.3) versus 2.2(0.2) days). Mean(s.e.m.) hospital stay was significantly reduced in the laparoscopic group (7.4(0.5) versus 12.6(2.5) days).

Conclusion Morbidity and mortality appeared to be reduced in patients undergoing laparoscopic stoma formation. The technique was found to be safe, suitable for the majority of patients and to give results superior to those of open surgery.

Minimally invasive surgery has had a major impact on many aspects of general surgery. A flurry of research was attempted to identify operations other than laparoscopic cholecystectomy¹ that may demonstrate similar advantages^{2–5}.

Creation of an intestinal stoma for defunctioning a distal segment of diseased bowel is a well established surgical practice. Conventional surgery, however, requires the patient to undergo a laparotomy. Current laparoscopic techniques spare the patient a large abdominal incision, minimize intraoperative intestinal handling and speed the postoperative recovery.

Experience in the authors' institution in a prospective study of laparoscopic stoma formation for faecal diversion is reported.

Patients and methods

Patients undergoing surgery for faecal diversion at this hospital between June 1991 and December 1995 were included in the study. Forty patients had a laparoscopic creation of stoma and 15 had open operation. Laparoscopic and open faecal diversion were performed by surgeons in the colorectal unit and open faecal diversion only was performed by surgeons from other surgical units during this period.

Only patients requiring faecal diversion for conditions such as those listed in Table 1 were included. All patients were evaluated before operation by a stoma therapist and the optimal stoma site was marked. Patients were informed of the procedure and those undergoing a laparoscopic procedure were informed of the possibility of conversion to an open laparotomy to complete the operation. Patients were starved for 6 h before operation but did not undergo bowel preparation. All patients underwent general anaesthesia with endotracheal intubation and received preoperative broad-spectrum antibiotics. All patients were positioned supine on the operating table.

Patients undergoing laparoscopy had placement of a 12-mm Hasson cannula using an open technique. Two 5-mm cannulas were placed under laparoscopic guidance in the suprapubic and right iliac fossa region for colostomy, or suprapubic and left iliac fossa region for ileal stomas. The appropriate loop of bowel was

identified using bowel graspers and mobilized as required. A circular trephine was made at the proposed stoma site and using Babcock forceps the bowel was grasped while held to the anterior abdominal wall. The proximal and distal limbs were noted and marked. The stoma was created in the usual manner using chronic catgut sutures as either an end or loop stoma. End stomas were created externally using a linear stapler across the bowel. The distal limb was then returned to the abdominal cavity. Patients undergoing open creation of a stoma underwent midline laparotomy. The appropriate loop of bowel was then mobilized as needed and a stoma created in the same manner.

Data are presented as mean(s.e.m.). The Mann–Whitney *U* test was used for comparison between the two groups and significance was accepted at $P < 0.05$.

Results

Between June 1991 and December 1995, 40 laparoscopic stomas were created. Fifteen open stomas were created during the same period. Table 1 lists the condition necessitating the diversionary stomas, operating time, time until flatus was passed, and hospital stay.

Complications occurred in seven of the 40 laparoscopic and six of the 15 open cases. One patient from each group experienced two complications (Table 2).

One patient in the laparoscopic group died. This patient was 91 years old with dementia; the stoma worked well but aspiration occurred and the patient died on day 8. Two patients in the open group died; an 87-year-old woman with disseminated rectal carcinoma died 12 h after operation. A 48-year-old man with extensive locally infiltrating transitional cell carcinoma of the bladder required stomal revision at 48 h, but he died on day 10 following a major pulmonary embolus.

Two patients were converted from laparoscopic to open procedures because of technical difficulties relating to extensive adhesions from previous surgery. The first patient, an 81-year-old woman with Dukes 'D' carcinoma of the rectum, was converted to open operation and total operating time was 120 min. Flatus passed on day 2 and total hospital stay for this patient was 6 days; she developed pneumonia in the postoperative period. The second patient was a 69-year-old woman with anal

Table 1 Data of patients undergoing faecal diversion

	Laparoscopic (n = 40)	Open (n = 15)	P*
Sex ratio (F:M)	20:20	6:9	
Age (years)†	65.2(2.1)	67.1(2.8)	0.7719
Operating time (min)†	54.3(4.7)	72.7(8.7)	0.0366
Time to flatus (days)†	1.6(0.3)	2.2(0.2)	0.0007
Hospital stay (days)†	7.4(0.5)	12.6(2.5)	0.0189
Morbidity	7	6	
Mortality	1	2	
Diagnosis			
Rectal carcinoma	23	8	
Anal carcinoma	6	1	
Other pelvic tumours	0	5	
Rectovaginal fistula	4	1	
Incontinence	2	0	
Dysmotility	2	0	
Crohn's disease	3	0	

†Values are mean(s.e.m.). *Mann-Whitney U test

Table 2 Diagnosis and morbidity of patients undergoing faecal diversion

	Laparoscopic	Open
Morbidity		
Pneumonia	1	2
Wound infection	1	2
Ileus prolonged	2	0
DVT/PE	1	1
Large stomal output	1	1
Small bowel obstruction	1	0
Stoma revised	0	1
Unspecified	1	0
Total	8	7

DVT/PE, deep venous thrombosis or pulmonary embolism

carcinoma. Total operating time was 40 min and she passed flatus on day 1; hospital stay was 5 days and she did not suffer any postoperative complication.

Discussion

Laparoscopic surgery has demonstrated significant advantages over open surgery. The majority of these patients are elderly, have inoperable tumours and in this high-risk group it is desirable to limit operative morbidity and mortality and to aid rapid return to the home environment. The present authors consider that laparoscopic surgery for these patients provides these benefits.

The laparoscopic technique does not impair the surgeon's ability to choose a stoma site and allows excellent visualization for mobilization of the bowel. Similar techniques have been described elsewhere^{6,7}.

The results reveal a conversion rate of 5 per cent. Only one other study has addressed laparoscopic diversional stoma; this found a conversion rate of 11 per cent⁸. The reduced operating time for laparoscopic cases compared with that for open cases is encouraging. This reflects the suitability of the procedure for surgeons experienced in

laparoscopic surgery and for the operation itself. As the study was addressing the new technique of laparoscopic stoma creation, the specialized unit adopted the technique in an attempt to compare with the open technique still being practised by all units. This could have resulted in bias in the present results. It may be said that the results would be expected to improve in the specialized unit for open or laparoscopic techniques.

Laparoscopic surgery minimizes postoperative ileus as indicated by the time to passage of flatus. These patients were able to resume normal diets earlier when they had laparoscopically created stomas. Others have reported quicker return of bowel function after laparoscopic techniques^{3,8,9}. Postoperative ileus was reduced in studies assessing the impact of laparoscopic cholecystectomy in dogs¹⁰. However, other studies have indicated that phase II myoelectric activity in bowel recovered with no differences between laparoscopic and open cases¹¹.

Patients were able to be discharged significantly earlier after laparoscopic operation, thereby reducing hospital costs. It is interesting to note that for both groups of patients hospital stay was often delayed because of inadequate inpatient stoma care ability and training. Improvements in prehospital and posthospital training of these patients might allow full advantage to be taken of the benefits of laparoscopic stoma creation.

Morbidity in the laparoscopic group was lower than in the open group and supports the documented benefits of laparoscopic surgery over open surgery^{2-5,9}.

In conclusion, laparoscopic stoma formation has significant advantages including reduced operating time and inpatient hospital stay. Morbidity and mortality appear to be reduced, making this an acceptable alternative to open stoma formation.

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Timing of surgery for fulminating pseudomembranous colitis

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Background With increasing antibiotic usage *Clostridium difficile* colitis is becoming more common. Surgery for fulminating *C. difficile* colitis, however, is rare because of the effectiveness of specific anticlostridial chemotherapy. Surgical outcome in five patients with fulminating *C. difficile* colitis involved in a recent outbreak of this disease is reported.

Methods Five of 138 patients developed fulminating *C. difficile* colitis unresponsive to medical therapy. All patients had antibiotics in the preceding period. Indications for operation in those who underwent surgery were systemic toxicity with a pyrexia, marked leukocytosis and abdominal signs leading to progressive organ failure, despite appropriate anticlostridial antibiotic therapy.

Results At operation all patients had a markedly oedematous colon with normal serosa but with acute mucosal colitis. All underwent subtotal abdominal colectomy and ileostomy. Progressive organ failure persisted in four, leading to death, giving a mortality rate of four in five in the operated group in comparison with 3.8 per cent (five of 133 patients) in those treated medically.

Conclusions These results indicate that this increasingly common disease frequently leads to a fatal outcome in patients requiring surgery and implies that earlier surgical consultation may be necessary to improve survival in patients with fulminating *C. difficile* colitis unresponsive to antibiotic therapy.

Clostridium difficile colitis is a nosocomial infection that is becoming increasingly common with the widespread use of antibiotics in hospital medicine. In the USA the number of cases diagnosed increased fivefold between 1986 and 1992¹. In the UK the number of reported cases to the Department of Health increased from 121 in 1982 to 3163 in 1993². *C. difficile* colitis has a broad spectrum of clinical presentation ranging from a mild diarrhoeal illness through pseudomembranous colitis to severe fulminant colitis with cardiovascular collapse and shock³. Since the advent of oral vancomycin there have been less than 50 incidences of patients with fulminant clostridial

colitis requiring surgery reported in the literature, with a collective mortality of 35 per cent⁴.

An outbreak of *C. difficile* colitis in 138 patients recently occurred in St James's Hospital, Dublin between January and July 1995. While the authors' experience may be anecdotal, the purpose of this report is to promote awareness of the clinical and operative features of this increasingly common condition and reflect on the poor outcome in patients who underwent surgery.

Patients and methods

An outbreak of *C. difficile* colitis occurred in this hospital with 138 positive toxin assays obtained during a 6-month period. The five patients reviewed in this report did not settle on medical

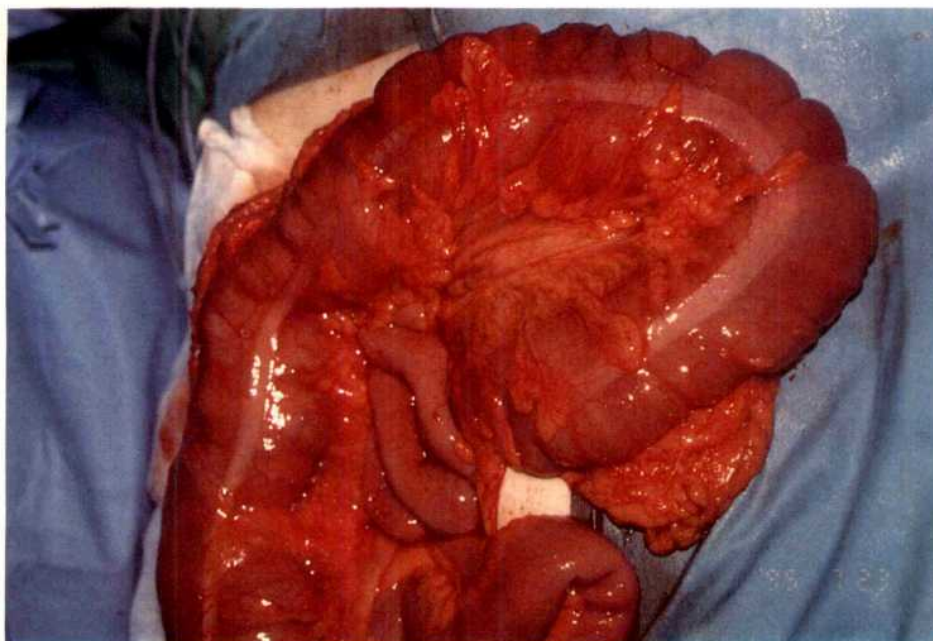


Fig. 1 Oedematous colon of a patient with pseudomembranous colitis at laparotomy (patient no. 5)

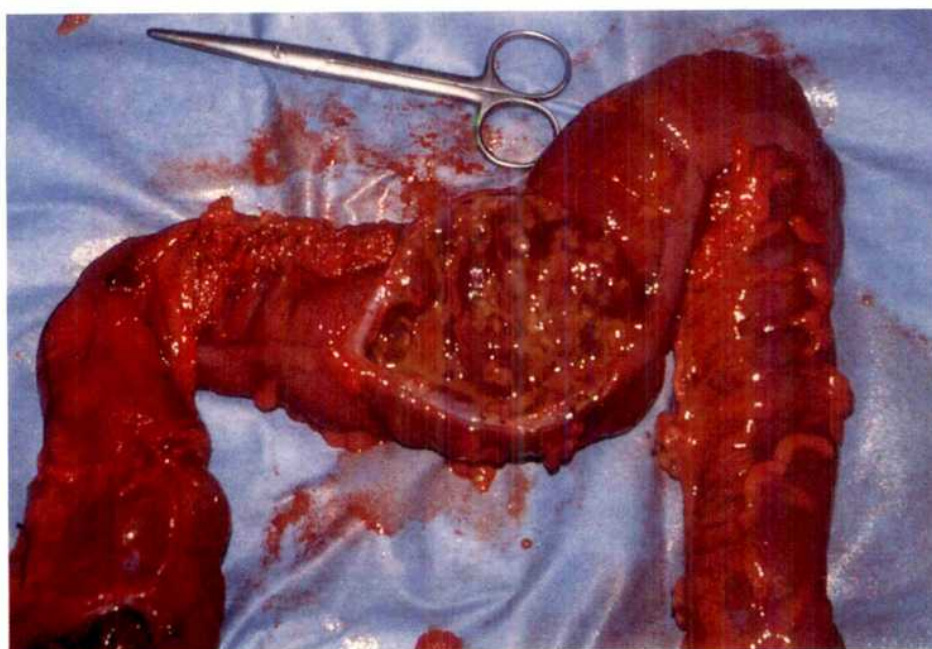


Fig. 2 Mucosal ulceration in a colectomy specimen (patient no. 5)

Table 1 Details of the five patients who underwent surgery for fulminating pseudomembranous colitis

	Patient no.				
	1	2	3	4	5
Sex	Female	Male	Male	Male	Female
Age (years)	75	72	80	73	46
Primary diagnosis	Acute exacerbation COAD	Acute exacerbation COAD	Fracture: neck of femur	Lung carcinoma	Acute colitis
Surgical history	None	None	Austin Moore prosthesis insertion	Lobectomy	None
Steroids	Yes	Yes	No	No	No
Preoperative diagnosis	Characteristic endoscopic appearance	Toxin positive	Toxin positive Endoscopic appearance	Toxin positive	Toxin positive Endoscopic appearance
Clinical signs					
Pyrexia	38°C	37.2°C	37.2°C	37.7°C	38°C
Abdominal signs	Distension and tenderness	Distension and tenderness	Distension and tenderness	Distension and tenderness	Distension and tenderness
Organ failure	CNS, renal, respiratory	CNS, respiratory	Renal, cardiac	Respiratory	CNS, renal, respiratory
Duration of symptoms (days)	20	17	9	28	5
White cell count ($\times 10^9/l$)	37.3	23.2	20.3	20.3	69
Previous antibiotic history	Cefotaxime 1 g t.d.s. $\times$ 11 days	Cefotaxime 1 g t.d.s. $\times$ 10 days	Cefuroxime 750 mg t.d.s. $\times$ 2 days and 250 mg b.d. $\times$ 5 days	Cefotaxime 1 g t.d.s. $\times$ 8 days Cefuroxime 250 mg $\times$ 6 days Cefotaxime 1 g t.d.s. $\times$ 1 day	Co-trimoxazole II b.d. $\times$ 7 days Erythromycin 250 mg q.d.s. $\times$ 7 days Tetracycline 250 mg q.d.s. $\times$ 5 days
Preoperative medical treatment	Vancomycin 1 g orally $\times$ 3 days Metronidazole 400 mg intravenously t.d.s. $\times$ 3 days	Metronidazole 400 mg intravenously t.d.s. $\times$ 7 days	Vancomycin 1 g orally $\times$ 3 days Metronidazole 400 mg intravenously t.d.s. $\times$ 3 days	Metronidazole 400 mg t.d.s. orally Vancomycin 1 g orally $\times$ 1 day	Tazocin intravenously $\times$ 2 days Gentamicin 80 mg intravenously t.d.s. $\times$ 2 days, metronidazole 400 mg t.d.s. orally $\times$ 1 day Vancomycin 1 g orally $\times$ 1 day

COAD, chronic obstructive airways disease; CNS, central nervous system; b.d., twice daily; t.d.s., three times daily

therapy and subsequently required surgery. The premorbid condition, risk factors, clinical course of these five patients are shown in Table 1. While comparison between the five patients operated on and the remainder of the group is difficult because of the small sample size it was noted that the mean (s.e.m.) age of the patients undergoing surgery was similar to the remainder of the group (69.2(4.5) versus 68.1(5.2) years. Nine of the 138 patients died. Four of five patients who underwent surgery died compared with five of 133 (3.8 per cent mortality rate) medically treated patients.

Indications for surgery were: (1) evidence of an acute abdomen with signs of peritonism; (2) systemic toxicity, i.e. shock; (3) multiple organ failure, especially respiratory and central nervous system failure leading to adult respiratory distress syndrome and confusion; and (4) progression of disease despite maximal appropriate anti *C. difficile* antibiotic therapy. Of the five patients operated on, four were *C. difficile* toxin-positive before surgery; two of these had relapses of previous episodes of diagnosed and treated clostridial colitis. Three patients had a sigmoidoscopy which showed the characteristic pseudomembranous appearance of *C. difficile* colitis. One patient had concurrent salmonella and clostridium infection.

At laparotomy all patients had ascites with a colon that was distended and markedly oedematous without overt signs of serosal inflammation (Fig. 1). On opening the colon after surgery there was severe mucosal ulceration in all patients (Fig. 2). All patients had a subtotal abdominal colectomy and ileostomy.

Results

Before operation, all patients required intensive care. The abdominal and gastrointestinal symptoms resolved in one patient; however, persistent respiratory difficulties led to respiratory failure and death at 3 months. Progressive multiple organ failure occurred in two patients and both died 3 and 5 days after surgery respectively. The fourth patient died from myocardial infarction 5 days after surgery. The fifth and youngest patient recovered fully.

Discussion

C. difficile colitis is increasing in incidence, possibly because of increases in antibiotic usage. While the use of specific ant clostridial therapy has reduced the mortality of this condition, some patients continue to deteriorate despite appropriate antibiotic therapy. Although the number of patients reported to have required surgical therapy for clostridial colitis is small (13 of 3300 in one study (0.39 per cent)³), the rate in this report is tenfold greater (3.6 per cent). This, allied to the high mortality rate of four in five as opposed to a collective mortality rate of 35 per cent in the literature in patients undergoing surgery, has prompted this report. While the reasons for this outbreak and high mortality rate are not clear, some conclusions can be drawn. It is possible that the virulence of the organism is changing or antibiotic resistance may be developing. Typing the organism in this outbreak has demonstrated that more than one strain was involved, implying that there was no single source of infection. Furthermore, as it is clear that some of these cases were community acquired, it is likely that this organism is endemic in at least our local community.

In this series the patients who developed severe clostridial colitis were mainly elderly. It is likely, therefore, that age and concurrent disease are major contributing factors to the high mortality rate in patients undergoing surgery for fulminating clostridium colitis. Interestingly, the one patient who did survive surgery was appreciably younger than those who died.

Cephalosporins have been implicated in the pathogenesis of this disease. However, this may reflect their widespread usage rather than a specific side-effect of this antibiotic. While three patients had therapeutic courses of antibiotics before the development of clostridial colitis, the fourth received a prolonged course of prophylactic antibiotics undergoing orthopaedic surgery. This illustrates the inherent dangers of prolonged chemoprophylaxis for many types of surgery and has led to changes in prophylactic antibiotic policies in this hospital. The fifth patient had received a number of different antibiotics from her GP for non-specific complaints in the months before admission, hence acquiring *C. difficile* infection in the community. With specific ant clostridial therapy *C. difficile* colitis has a relapse rate of 25–30 per cent⁶. Two of the patients reported here had previous *C. difficile* colitis episodes treated successfully, which emphasizes the importance of follow-up in these patients.

The majority of patients acquiring *C. difficile* colitis respond adequately to medical treatment. The authors' experience suggests that surgery is indicated by the following: (1) evidence of abdominal signs; (2) systemic toxicity; (3) multiple organ failure; and (4) progression of symptoms despite maximal appropriate antibiotic therapy. Most recent reports clearly suggest that total abdominal colectomy and ileostomy is the surgical treatment of choice for patients with unresolving clostridial colitis⁵. All patients in this series had radical surgery and, in addition, three patients had a distal mucous fistula formed to allow irrigation of the rectal stump with appropriate antibiotics.

Lack of appreciation of the fatality of this condition may have played a role in the poor results of surgery in this series. It is interesting to note that the single survivor in this series was the last patient to present when awareness of the necessity for radical and early surgery was at its highest. Experience, therefore, would indicate that with fulminating *C. difficile* colitis early consultation, possibly joint medical and surgical management, and earlier recourse to surgery before the development of multiple organ failure may improve survival in this potentially fatal condition.

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The authors thank Professor T. P. J. Hennessy and Mr R. Stephens for allowing them to include their patients in this report.

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Transanal self-expanding metal stents as an alternative to palliative colostomy in selected patients with malignant obstruction of the left colon

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Background Palliative colostomy is still unavoidable in many patients with malignant obstruction of the left colon. This report describes an initial experience and follow-up in a small series of patients with left-sided colon obstruction in whom transanal self-expanding metal stent (SEMS) placement was attempted for palliative purposes.

Methods Palliative transanal SEMS placement was attempted in 11 patients with malignant obstruction of the rectosigmoid region. The selection criteria included patients with advanced pelvic disease, peritoneal carcinomatosis and/or multiple parenchymatous metastatic disease. Wallstent oesophageal endoprotheses were used, and the technique was carried out by interventional radiologists.

Results The technique succeeded in relieving the obstruction in seven patients, and surgical intervention was prevented in six. Five of these six patients died with an unobstructed colon from 26 days to 7 months after SEMS placement. The technique failed in four patients, three of whom underwent emergency colostomy.

Conclusion Transanal SEMS placement is an appealing method for the relief of obstruction in selected patients, obviating the need for palliative colostomy.

The surgical management of malignant left-sided colonic obstruction has changed considerably in recent years, with many authors now advocating a single-stage procedure^{1,2}. Nevertheless, the creation of a colostomy is still unavoidable in this setting in many cases, as part of Hartmann's procedure, in high-risk and debilitated patients unsuitable for more aggressive treatment, or when the surgeon encounters irresectable advanced pelvic disease, peritoneal carcinomatosis or diffuse parenchymatous metastatic disease. These colostomies may be permanent in many cases, causing considerable distress in patients with a short life expectancy. Colostomy formation itself may also have an associated morbidity and mortality.

The use of a self-expanding metal stent (SEMS) to relieve colorectal malignant obstruction has been described recently, both for palliative purposes and to allow delayed elective surgery after mechanical bowel preparation^{3–6}. This report describes the authors' initial experience and follow-up in a small series of patients with malignant obstruction of the left colon, in whom transanal SEMS placement was attempted for palliative purposes.

Patients and methods

The level of obstruction was determined by water-soluble Gastrografin (Schering, Berlin, Germany) and only patients with obstruction in the rectosigmoid region were considered for therapy. In case of successful decompression of the bowel with

this technique, patients were not considered for elective surgery if they fulfilled any or all of these selection criteria: high-risk and debilitated patients unsuitable for more aggressive therapy, advanced pelvic disease, peritoneal carcinomatosis and multiple parenchymatous metastatic disease. After informed consent had been obtained from the patients, the technique was carried out by interventional radiologists, following the steps described recently by Tejero *et al.*^{4–6}. Wallstent oesophageal endoprotheses (Schneider, Büllach, Switzerland), 22 mm in diameter and 70–100 mm in length, were used in all cases. A preshaped 7-Fr angiographic catheter (Cordis, Miami, Florida, USA) and a 0.038-inch angled stiff-type Glidewire (Terumo, Tokyo, Japan) were jointly advanced through the anus to the tumour under fluoroscopic guidance. The stenosis was then negotiated with the Glidewire and angiographic catheter. Once the lesion had been traversed, the Glidewire was replaced by a 0.038-inch Amplatz Superstiff guidewire (Medi-Tech/Boston Scientific, Watertown, Massachusetts, USA) (Fig. 1). The angiographic catheter was then withdrawn and the delivery system of the endoprosthesis was advanced over the Amplatz guidewire through the tumour. After deployment of the stent, contrast material was injected to assess the patency and correct location of the stent (Fig. 2). The time required for the procedure varied between 15 min and 1 h, and no anaesthesia or sedation was necessary; after this time, in case of failure of the technique, the procedure was abandoned and the patient underwent emergency laparotomy. Endoscopic assistance was not available during this initial experience.

Some 48 h after successful SEMS placement a further Gastrografin enema was performed to assess the patency of the stent and to rule out complications. Staging of the tumour was carried out and consideration given to palliative chemotherapy. Patients had an early discharge from hospital and were instructed to report to some of the authors in case of recurrence of the abdominal distension and/or severe constipation. Two of them were seen as outpatients after 2 months, and had a contrast enema (Fig. 3).

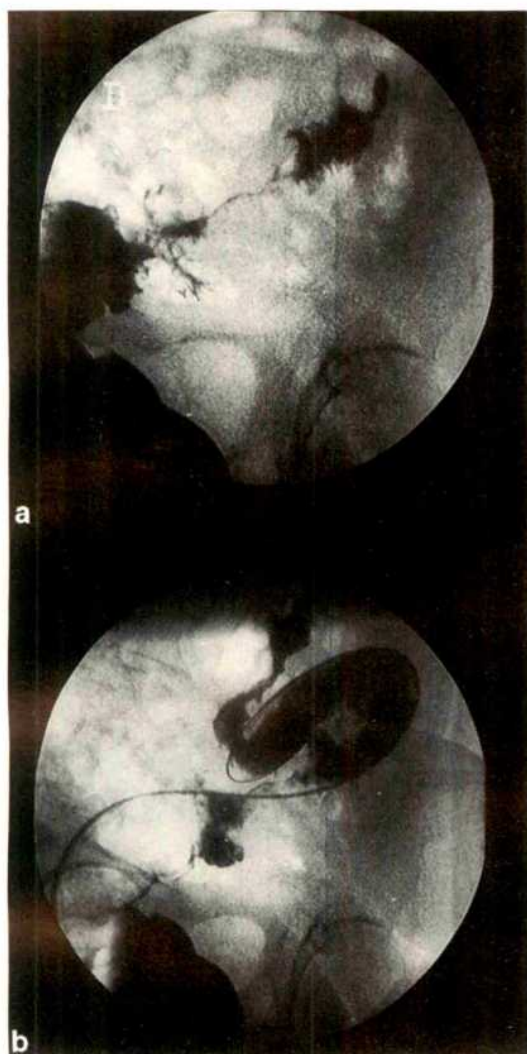


Fig. 1 a Gastrografin enema showing stenosis causing an obstruction at the rectosigmoid junction. b The lesion has been traversed and the Guidewire replaced by an Amplatz Superstiff guidewire

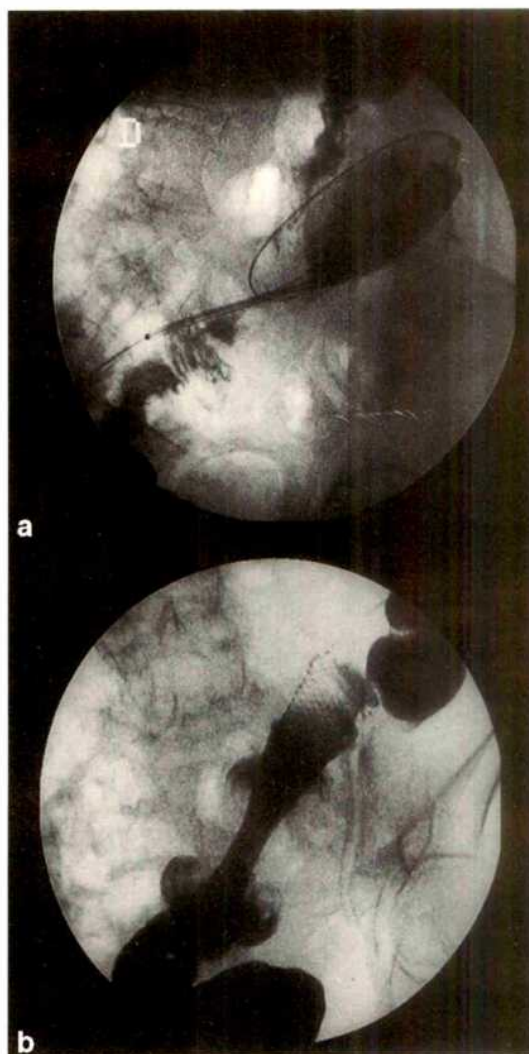
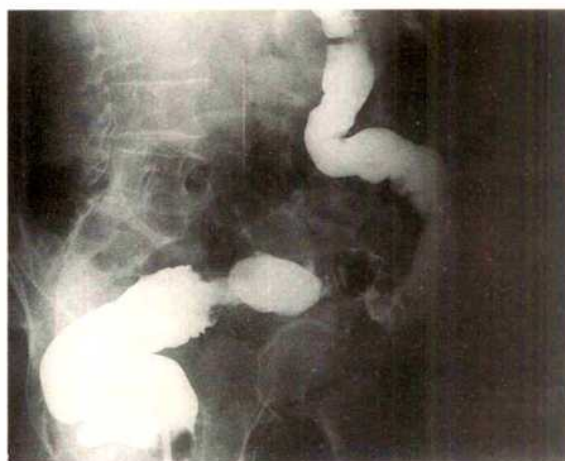


Fig. 2 a The delivery system of the endoprosthesis has been advanced over the Amplatz guidewire through the tumour. b The stent has been deployed



a



b

Fig. 3 a The stent is fully deployed at 48 h. b Contrast enema at 3 months

Results

From April 1995 to March 1996, palliative SEMS placement was attempted in 11 patients (six men) of mean age 66 (range 47–83) years with malignant obstruction of the rectosigmoid colon. In six patients computed tomography staging was done on an emergency basis to rule out disseminated disease and as part of a current study protocol comparing SEMS placement and delayed surgery with emergency single-stage resection. Two of the 11 patients had low-grade obstruction, and all the others presented with an acute high-grade or complete obstruction. In eight patients the acute obstruction was the primary manifestation of the disease, and the others were recurrences.

The technique succeeded in relieving the obstruction in seven patients; signs and symptoms of intestinal obstruction resolved within 24 h of SEMS placement in six of these; in the remaining patient, and although some improvement was evident from the start, complete clinical and radiological resolution did not occur until the fourth day.

Surgical intervention was prevented in six patients. The remaining patient underwent palliative sigmoid colectomy shortly afterwards because of the preference of his attending surgeon. This patient survived for 5 months. Five of the six patients treated non-surgically died with an unobstructed colon between 26 days and 7 months after SEMS placement. The other patient is alive and receiving palliative chemotherapy 6 months after placement of two stents because of the length of the obstructive lesion; she complains of scant bleeding with bowel movements and needs laxatives. One patient had an anastomotic stenosis 10 cm from the anal verge, with pseudo-obstructive symptoms and severe tenesmus. Following SEMS placement, the pseudo-obstructive symptoms were much improved, but the tenesmus seemed to be worse. During his 6 months' survival, this patient was readmitted twice because of severe tenesmus and was offered a colostomy, which he refused.

In four patients the procedure was unsuccessful in relieving the obstruction. All of them had a 'cut-off' sign on the Gastrografin enema, with no proximal progression of any contrast material beyond the obstruction. One of these patients underwent a further attempt at SEMS placement with colonoscopy, to no avail. Three of them underwent an emergency diverting colostomy, with a poor outcome: one died from acute postoperative renal failure, and another had severe abdominal necrotizing fasciitis originating in the colostomy. The remaining patient underwent emergency subtotal colectomy and ileorectal anastomosis; he suffered anastomotic breakdown and ileostomy was performed.

Discussion

The poor condition of some patients with acute malignant obstruction of the left colon, and/or the finding at the emergency laparotomy of peritoneal carcinomatosis, irresectable advanced pelvic disease and/or multiple parenchymatous metastatic disease, makes the performance of colostomy the only reasonable, and unavoidable, technical option.

Survival of patients with advanced metastatic colorectal cancer depends on the nature and extent of the metastatic disease; the survival time of patients with bilobar liver metastases ranges from 8.5 to 12 months in most series⁷. The outlook is even worse in patients presenting with

obstruction and synchronous metastatic disease, and it is generally accepted that palliative resection is futile in terms of survival when liver or peritoneal deposits are present⁸. This has led to the increasing use of interventional techniques in the palliation of disease in these patients, in an attempt to avoid colostomy and to improve the quality of life^{9–11}.

Although the use of expanding metal stents in the palliation of malignant obstruction in the gastrointestinal tract has been reported extensively in recent years^{12,13}, Itabashi *et al.*³ were the first to report its scheduled use in the palliative treatment of rectosigmoid strictures caused by irresectable recurrent neoplasm in two patients. Recently, Tejero *et al.*^{4–6} used this technique on an emergency basis in completely obstructing lesions. These authors do not report technical failures (i.e. inability to cross the obstruction or to negotiate a tortuous recto-sigmoid region), which occurred frequently in the present series, although they seem to have used only fluoroscopic guidance, without endoscopy⁶. It is not clear whether they focused only on successful cases but, in view of the present authors' rather high failure rate, a combined approach using endoscopic and fluoroscopic guidance is currently being assessed. The potential advantages of this expensive technology are yet to be demonstrated in patients who prove to have a resectable lesion after staging of the tumour or after laparotomy. However, in patients who receive palliative treatment only, because of inoperability or extremely poor prognosis, successful decompression by means of transanal SEMS placement has many potential advantages and could improve the quality of life, provided it is durable, well tolerated and with a low complication rate. SEMS placement can obviate the need for colostomy, which is usually done under general anaesthesia, and its attendant morbidity and mortality, and can also considerably shorten the hospital stay. To select, in the emergency situation, patients amenable to palliative transanal SEMS decompression, the performance of urgent tumour staging by computed tomography could be of great help.

A potential indication for this technique was assessed in the two patients with a so-called low-grade or incomplete obstruction, or severe obstructive constipation. These patients are sometimes offered scheduled palliative colostomy in an attempt to alleviate symptoms and/or prevent an impending complete obstruction. The placement of a SEMS can be useful and is technically easier in these cases, and probably merits further investigation.

Two patients with SEMS placed low in the rectum complained of severe tenesmus. At this level both the tumour and the stent can produce this disabling symptom, and balloon dilatation and laser recanalization would probably offer better palliation if colostomy is to be avoided.

It can be concluded from this initial experience that palliative transanal SEMS placement is an appealing method in selected patients, obviating the need for palliative colostomy. It remains to be assessed whether simultaneous sigmoidoscopic assistance might increase the success rate of the technique and enable SEMS placement in more proximal lesions.

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Experimental study of the effect of preoperative 5-fluorouracil on the integrity of colonic anastomoses

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Background Despite curative resection for colorectal cancer, many patients develop recurrence at the primary site or distant organs. These patients are candidates for (neo)-adjuvant chemotherapy. Very little is known about the effect of preoperative 5-fluorouracil (FU) on the healing of colonic anastomoses. The aim of this study was to assess this in a rat model.

Methods Eighty male Wistar rats, weighing 160–215 g, were divided into three groups; (1) a control group underwent left colon resection and primary anastomosis ($n = 20$); (2) a sham group received 1 ml saline intraperitoneally ($n = 30$); (3) a study group received 5-FU intraperitoneally (20 mg kg^{-1}). Both saline and 5-FU injections were given intraperitoneally for 5 days before operation.

Results There was no difference in the rate of wound complications, intraperitoneal adhesions and anastomotic complications among the groups. Three and seven days after operation, mean bursting pressure of the anastomosis was 36.5 and 198 mmHg in group 1, 34 and 200 mmHg in group 2, and 39 and 190 mmHg in group 3 respectively (P not significant). Although the myeloperoxidase and hydroxyproline content were significantly lower after 5-FU therapy ($P < 0.01$, compared with others), the clinical outcome was similar.

Conclusion Preoperative 5-FU for 5 consecutive days before operation had no effect on the healing of colonic anastomoses.

Despite curative resection for colorectal cancer, many patients develop recurrence at the primary site or distant organs. Neoadjuvant chemotherapy may be beneficial in some patients. 5-fluorouracil (5-FU) has been used either alone, with other chemotherapeutic agents or in combination with radiotherapy as an adjuvant to reduce the risk of recurrence¹.

Perioperative use of cytostatic agents causes a delay in wound healing and increases the chance of wound dehiscence, possibly because of an inhibition of collagen synthesis^{2,3}. As a result, adjuvant treatment is usually withheld, until the wound is healed. However, to improve outcome, there is still a strong biological rationale for earlier systemic chemotherapy.

Operative manipulation can increase circulating malignant cells. Preoperative chemotherapy may improve the resectability of a neoplasm or reduce the incidence of distant metastases or local recurrence^{4,5}. Because of these theoretical advantages, neoadjuvant chemotherapy may be a new prospect for colorectal cancer treatment. This study investigated the effect of preoperative 5-FU on the healing of colorectal anastomoses in the rat.

Materials and methods

Eighty male Wistar rats with a median weight of 200 (range 160–215) g were used. All animals were weighed daily and had free access to a standard laboratory diet and water. There were three groups: (1) a control group ($n = 20$); (2) a sham group ($n = 30$) which received saline intraperitoneally and (3) a study group ($n = 30$) which received 5-FU intraperitoneally. Intraperitoneal injections were given for 5 days before operation, the last injection was given 3 days before operation. 5-FU 5 mg ml^{-1} was given as an injection intraperitoneally in a daily dose of 20 mg kg^{-1} . Saline was given at a corresponding volume to the

sham group. Within each group one-half of the animals were studied 3 days and one-half 7 days after the operation. After the animals were killed, blood samples were obtained from the inferior vena cava for haemoglobin concentration and white cell count estimation.

Operative procedures

Three days after completion of injections, the animals were anaesthetized with an intraperitoneal injection of 10 mg kg^{-1} sodium phenobarbital (I.E. Ulagay, Istanbul, Turkey) in sterile water. A 1-cm left colon resection was performed 2 cm above the peritoneal reflection through a mid-line incision. Bowel continuity was restored with an end-to-end anastomosis of 10–11 interrupted sutures (6/0 monofilament polypropylene; Serapen, Bayern, Germany). The abdominal muscle layers and skin incision were closed separately with running sutures (4/0 silk, Doğan, Trabzon, Turkey). All procedures were done by one surgeon. One-half of the animals in each group were anaesthetized again either on day 3 or 7 after operation for *in vivo* analytical procedures. The animals were then killed by haemorrhage for *in vitro* analytical procedures.

Analysis

Wound complications, intestinal obstruction and anastomotic complications were recorded. Intraperitoneal adhesions were graded according to Knightly *et al.*⁶: grade 0, no adhesions; grade 1, a single, thin easily separable adhesion; grade 2, less extensive but weak adhesions which stood the traction poorly; grade 3, numerous extensive visceral adhesions which involved the parietal extensions; grade 4, numerous extensive dense adhesions which involved the adjacent mesentery, intestine, omentum, extending to the abdominal wall. Anastomotic stenosis was defined if the ratio of the width of bowel proximal and distal to the anastomosis exceeded 2. The strength of each anastomosis was assessed by measuring its burst pressure using a fluid pump (Becton Dickinson, Breda, France), operating at 5 ml min^{-1} with a pressure transducer (Abbott Monitoring Kit (Transpac II), Abbott Ireland, Sligo, Ireland). A catheter was passed via the rectum, to 2 cm below the level of anastomosis. The colon was

Table 1 Complications

Group	n	Wound infection	Wound dehiscence	Intestinal obstruction	Anastomotic stenosis	Anastomotic dehiscence
Control	20	3	—	—	—	—
Saline	30	3	2	1	1	—
5-fluorouracil	30	2	1	—	—	1*

*Closed perforation without any signs of peritonitis *P* not significant between the groups

ligated around the catheter below and also 2 cm proximal to the anastomosis. The pressure was recorded in mmHg using a monitor (Petaş KMA 260R, Ankara, Turkey). Burst pressure was therefore measured *in situ* without disturbing any adhesions formed around the anastomosis. To assess the effect of 5-FU on a normal segment, burst pressure measurement was done in the left colon 4 cm above the anastomosis. The pressure was observed, and the site of leakage was visualized with a magnification lens or identified by a sudden loss of pressure. After the burst strength test, the animals were killed by haemorrhage. The anastomotic segment was isolated from the surrounding tissue and resected for hydroxyproline assay as a

marker of collagen content and for myeloperoxidase activity as a marker of leucocyte accumulation^{7,8}.

Differences between groups were evaluated using one-way analysis of variance (ANOVA). *P* < 0.05 was considered significant.

Results

The effects of preoperative 5-FU on abdominal wound healing and anastomotic complications are shown in Table 1. No significant effect was detected. Animals treated with intraperitoneal 5-FU had lost significantly more weight than the other groups (Fig. 1). No significant differences were found either in anastomotic or normal colonic burst pressures between the three groups (Fig. 2). However, both myeloperoxidase (Fig. 3) and hydroxyproline (Fig. 4) content were significantly lower following chemotherapy when compared with other groups.

All 3-day-old anastomoses burst at the suture line in all groups. In the 7-day-old colonic segments rupture was noted outside the anastomosis in all animals, except one in each control and 5-FU groups respectively (*P* not significant).

The median adhesion scores according to Knightly *et al.*⁶ were 1.9 (range 1–4), 1.8 (range 1–4), 1.6 (range 1–3) in control, saline, and 5-FU groups respectively (*P* not significant).

The haemoglobin concentration did not differ between groups during the study. The white blood cell count was similar in all groups but reduced on day 7 in animals receiving 5-FU intraperitoneally (3.8 (range 1.8–4.4)

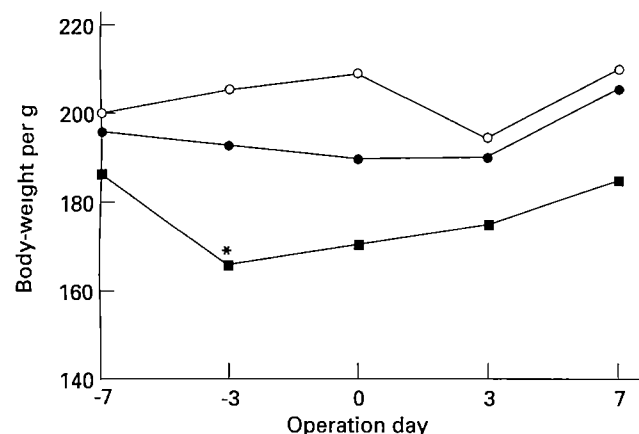


Fig. 1 Weight measurement during the experiment. ○, Control; ●, saline; ■, 5-fluorouracil (5-FU) *Reduction was significant in the animals treated with 5-FU (*P* < 0.01)

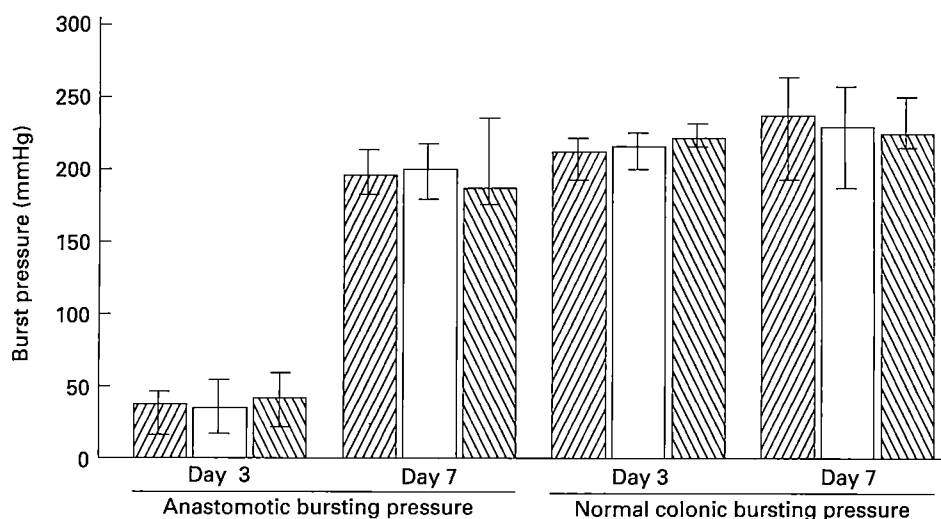


Fig. 2 Median (interquartile range) anastomotic and normal colon burst pressures on days 3 and 7 after operation. ▨, Control; □, saline; ▤, 5-fluorouracil

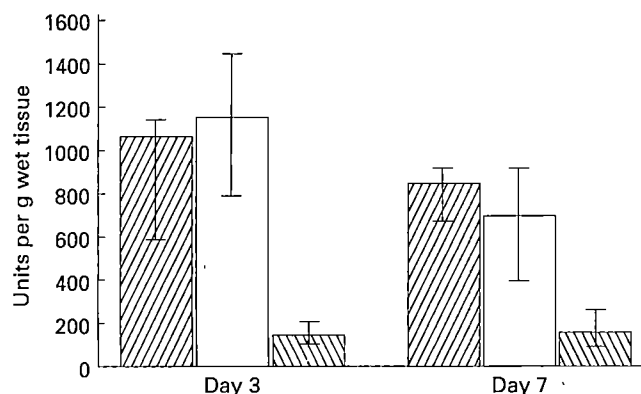


Fig. 3 Median (interquartile range) myeloperoxidase activity was significantly lower after instillation of 5-fluorouracil (▨) when compared with control (▧) and saline (□) groups on days 3 and 7 after operation ($P < 0.001$)

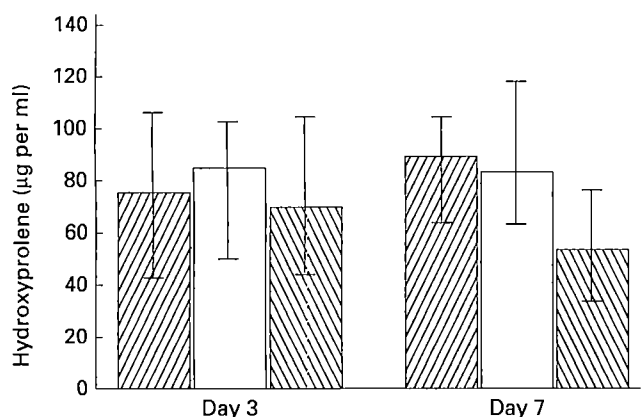


Fig. 4 Median (interquartile range) hydroxyproline content was significantly lower after instillation with 5-fluorouracil (▨) on day 7 after operation compared with other groups. ▧, Control, □, saline ($P < 0.01$)

10^9 l^{-1} versus 5.4 (range $3.5\text{--}7.4$) in the saline group and 4.8 (range $2.3\text{--}7.2$) in controls; $P < 0.01$ 5-FU versus control).

Discussion

High recurrence rates following curative resection for colorectal cancer have prompted investigation of chemotherapy as an adjunct. The results for both systemic and intraperitoneal administration of 5-FU have been encouraging^{9–11}. As high systemic drug concentrations result in toxic effects, 5-FU has been given intraperitoneally. The high local concentration may provide pharmacokinetic and therapeutic advantages by killing all micrometastases, especially at the resection site and peritoneal surfaces which are at high risk for local recurrence. A prospective trial showed that 5-FU intraperitoneally reduced peritoneal failure significantly better than intravenous 5-FU¹². In addition, previous clinical and experimental studies have shown that immediate postoperative 5-FU given intraperitoneally has no adverse effect on outcome^{13,14}; 5-FU was therefore used as a neoadjuvant therapy in the present study.

A recent study showed that preoperative administration of 5-FU once a week starting 4–6 weeks before operation, had no effect on the healing of colonic anastomoses¹⁵. As surgery is the main treatment for gastrointestinal malignancy, such a delay before operation is not ideal. To maximize the effect of chemotherapy the authors used 5-FU for 5 consecutive days before the operation which is more likely to resemble possible clinical protocols and differentiated the present study from those previously carried out.

In the present study the frequency of abdominal wound and anastomotic complications was significantly lower than when 5-FU was given immediately after operation³. The 3-day gap between the operation and the last day of chemotherapy may be responsible for reducing the harmful effects of immediate treatment¹⁶.

Weight reduction was detected both during 5-FU injections and after operation, but did not affect outcome suggesting that anastomotic healing is likely to be independent of malnutrition as reported by others^{17,18}.

The anastomotic burst pressure and site was similar among all groups in the present study. The burst pressure of 7-day-old anastomoses was similar to normal colon. Since anastomotic burst pressures were measured *in vitro* in most previous similar reports, the present study is more likely to reflect the clinical situation as it was performed on live animals^{3,14–16}.

The myelosuppressive action of 5-FU is most frequently manifested as leucopenia, the nadir of which is usually between the 9th and 14th day after the first injection of the drug¹⁹. This is in agreement with the findings that anastomotic myeloperoxidase activity on both days 3 and 7 after operation was significantly lower after 5-FU compared with the other groups. Despite this, burst pressure, anastomotic complications and the clinical outcome were similar. The importance of anastomotic myeloperoxidase activity as a marker of leucocyte accumulation remains unclear with respect to wound healing. Similarly, despite a recent study which showed that basal and transforming growth factor β stimulated collagen synthesis remained unaffected by 5-FU in tissue cultures²⁰, anastomotic hydroxyproline content was reduced on day 7 in rats treated with 5-FU in the present study.

In the present study there was no adverse effect of preoperative chemotherapy on anastomotic healing and burst pressure. This and previous studies were performed on healthy animals and may not reflect the situation in the case of malignant tumours^{2,3,14–16,18}. These experiments need to be confirmed in animals with colonic tumours.

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Functional results after transanal rectal advancement flap repair of trans-sphincteric fistula

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Background Transanal rectal advancement flap repair is an operation to treat trans-sphincteric fistula which leaves the external sphincter muscle essentially untouched. Anal sphincter function was evaluated prospectively before and after this procedure.

Methods Anorectal manometry was performed in 24 patients before operation and 3 months after surgery. A detailed standardized questionnaire on faecal continence was answered before surgery, then at 3 and 48 months after surgery.

Results No significant differences were seen between mean(s.e.m.) preoperative and postoperative values for maximum squeeze pressure (100.0(9.7) versus 118.0(12.7) mmHg), maximum resting pressure (56.6(4.3) versus 52.8(4.1) mmHg), rectal compliance (4.4(0.6) versus 3.5(0.5) ml/mmHg) or any other parameter of anorectal manometry. The questionnaire revealed the occurrence of minor incontinence in two patients following surgery, which remained unchanged for 4 years. Three other patients had continence disturbances 4 years after surgery which were probably unrelated to the procedure.

Conclusion In addition to high success rates, transanal rectal advancement flap repair also yields excellent functional results. This procedure should be performed for trans-sphincteric fistula in place of alternative treatments whenever feasible.

Symptomatic perianal fistulas are traditionally treated by the 'laying open' technique¹, fistulectomy² or seton drainage^{3–5}. For trans-sphincteric fistula, an alternative technique called transanal rectal advancement flap repair has been advocated in recent years⁶. Low recurrence and low morbidity rates after this procedure have been documented for uncomplicated⁷ and complicated⁸ fistulas, as well as for fistulas in the context of Crohn's disease^{9,10}. In contrast, the impact of transanal advancement flap repair for trans-sphincteric fistulas on faecal continence has rarely been investigated closely.

The aim of this study was to evaluate the functional results prospectively before and after this procedure by anorectal manometry and with a detailed standardized questionnaire.

Patients and methods

Patients

Twenty-four consecutive patients who underwent transanal rectal advancement flap repair between November 1991 and June 1993 were evaluated prospectively (ten men and 14 women of median age 38 (range 25–66) years) (Table 1). Eight patients had a colostomy at the time of surgery. All patients were suffering from a symptomatic trans-sphincteric fistula. Patients who had further anorectal disorders such as anal fissure, haemorrhoids or congenital abnormality were excluded from the study.

Initially, transanal advancement flap repair was successful in 20 patients. In three patients with Crohn's disease and one without, closure of the fistula was unsuccessful. However, in these patients the operation was repeated successfully. After 4 years (range 43–59 months) of follow-up, relapse occurred in 9 of the 24 patients (seven of 16 patients with and two of eight without Crohn's disease) with a median disease-free interval to fistula recurrence of 9 (range 4–40) months.

Surgical technique

As described previously⁹, transanal rectal advancement flap repair was performed according to the technique of Lewis and Bartolo⁶.

Anorectal manometry

Standard anorectal manometry was performed as reported previously¹¹.

Standardized questionnaire

The status of anal continence before surgery and at 3 months after operation was documented by a standardized questionnaire, as described previously¹¹. As seven patients had a colostomy 3 months after surgery, they could not report on physiological defaecation. Consequently, the questionnaires only of the remaining 17 patients were evaluated. Some 4 years after surgery (median 48 (range 43–59) months) the questionnaire was repeated by telephone. Contact was established with 21 patients. One patient still had a colostomy. In total, 20 questionnaires were available for evaluation.

Table 1 Description of fistulas and previous treatments

	Patients with Crohn's disease (n = 16)	Patients without Crohn's disease (n = 8)
Fistula description		
Multiple fistulas	7	3
Anovaginal fistula	10	8
Mean duration of fistula (years)	4.2	1.8
Previous treatment		
Seton drainage	12	6
Fistulotomy or fistulectomy	13	5
Abscess drainage	10	4
Anal canal reconstruction	3	0

Statistical analysis

Differences between preoperative and postoperative results of anorectal manometry were assessed by the Wilcoxon test, with the exception of the rectoanal inhibitory reflex which was evaluated by McNemar's test. McNemar's test was also used to assess the results of the preoperative and postoperative questionnaires.

Results

Anorectal manometry

No differences between preoperative and postoperative values were observed for any parameter assessed (Fig. 1 and Table 2).

Standardized questionnaire

Questionnaire data are summarized in Table 3. Fourteen of 17 patients evaluated were completely continent before surgery. Two of these patients reported occasional incontinence to gas and liquid stools 3 months after operation. Three patients partially incontinent to liquid stools and gas before operation remained unchanged 3 months after surgery.

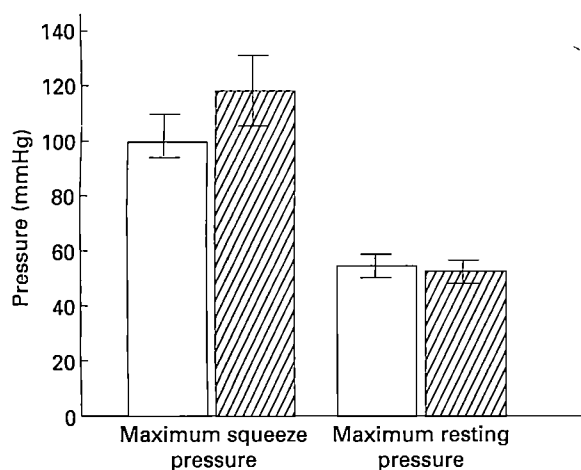


Fig. 1 Results of anorectal manometry. Values are mean(s.e.m.). □, Before operation; ▨, 3 months after operation. No significant differences were observed between preoperative and postoperative values

Table 2 Results of anorectal manometry

	Before operation	3 months after operation
No. of patients with rectoanal inhibitory reflex	17	12
Distension volume at rectoanal inhibitory reflex (ml)*†	21.2(2.7)	20.0(3.3)
First sensation at rectal distension (ml)*	40.8(2.9)	48.5(4.2)
Pain at rectal distension (ml)*	167.1(17.4)	165.6(19.2)
Compliance (ml/mmHg)*	4.4(0.6)	3.5(0.5)
Functional length of anal canal (cm)*	3.8(0.1)	3.6(0.2)

Values are *mean(s.e.m.). †Only if present until 50-ml distension volume reached

Table 3 Results of the standardized questionnaire

	Before operation (n = 17)	After operation	
		3 months (n = 17)	4 years (n = 20)
Daily frequency of bowel movements			
1–3 per day	11	10	14
4 or more per day	6	7	7
Complete continence			
Gas	14	12	17
Liquid stool	14	12	15
Solid stool	17	17	20
Use of sanitary pads	6	7	9
Ability to defer defaecation for more than 5 min	10	12	14
Sensory discrimination of stool	9	8	12

After 4 years, alterations of sphincter function had occurred in three patients who were all unchanged 3 months after transanal advancement flap repair. One patient reported incontinence to gas and liquid stools as well as soiling and requiring sanitary pads. Several months after undergoing flap repair, the fistula had recurred and the patient went to a different hospital for a fistulotomy. Minor impairment of continence was present in the other two patients. One had a reduced ability to delay bowel movements for more than 5 min without actual incontinence. This patient, in the meantime, had undergone colectomy with ileorectal anastomosis, which may account for the slight impairment of faecal continence. Another patient reported soiling and requiring sanitary pads. The reasons for this could not be clarified.

Discussion

Transanal rectal advancement flap repair has become an increasingly popular operation for the treatment of trans-sphincteric fistula^{6–9}. After this procedure, low recurrence rates have been documented for trans-sphincteric fistula in the context of Crohn's disease^{9,10}, as well as for fistulas unrelated to Crohn's disease⁷.

In the present study no change in sphincter function could be detected by anorectal manometry before and 3 months after flap repair. However, two patients reported minor impairment of continence 3 months after operation. These good functional results were substantiated by a long-term follow-up questionnaire after 4 years. Although nine of the 24 patients had fistula recurrence, only three reported changes in faecal continence. In two of these cases, continence impairment was not attributable to transanal advancement flap repair and in the other case the origin remained unknown. This demonstrates that sphincter function is usually preserved immediately after flap repair and generally persists over the years, even if the fistula recurs.

In the present patients, a U-shaped incision was performed to raise the flap. Consequently, undue damage to the internal sphincter, with a subsequent reduction in maximum resting pressure, was probably avoided. Similar results were reported by Lewis *et al.*¹² in a series of nine patients. In contrast, a decrease in maximum resting pressure and decreased continence were reported in 21 per cent of patients when internal sphincterotomy was added to the flap repair¹³.

Traditional treatments such as laying open the fistula tract or fistulectomy are inadvisable for 'high' trans-sphincteric fistulas because partial or complete transection of the external sphincter muscle is unavoidable^{1,2}. This has detrimental effects on faecal continence. In contrast, more conservative treatment with setons shows a great variability in terms of functional outcome^{3,4} which is probably due to different technical modifications^{5,14}. In addition, seton treatment generally entails an enduring follow-up and only limited success, particularly in patients with Crohn's disease.

In conclusion, transanal rectal advancement flap repair for trans-sphincteric fistula yields excellent functional results, which are likely to be superior to those of alternative procedures and to persist even if the fistula recurs. Consequently, this operation can be recommended even if the recurrence rate is increased as, for example, in patients suffering from Crohn's disease. The authors believe that transanal rectal advancement flap repair is the treatment of choice for trans-sphincteric fistula.

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Cutting seton *versus* two-stage seton fistulotomy in the surgical management of high anal fistula

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Background The aim of this study was to compare the clinical results obtained with the cutting seton and the two-stage seton fistulotomy (TSSF) in the surgical management of high anal fistula.

Methods The case records of 59 patients with high anal fistula of cryptoglandular origin treated with cutting seton ($n = 12$) or TSSF ($n = 47$) over a 5-year period were retrospectively reviewed. There was no difference between the groups in age, sex distribution, or estimated percentage of anal sphincter involved by the fistula. Follow-up was by a mailed questionnaire inquiring about fistula recurrence, incontinence, and degree of satisfaction. Mean follow-up was similar in both groups (27 months for cutting seton *versus* 33 months for TSSF). Comparisons were made by Student t and χ^2 tests, as required.

Results There were no differences in the rate of fistula recurrence between the groups treated with cutting seton or TSSF (one of 12 *versus* four of 47), difficulty holding gas (six of 12 *versus* 25 of 47), underwear staining (six of 12 *versus* 18 of 47), stool incontinence (three of 12 *versus* 12 of 27), overall incontinence (eight of 12 *versus* 31 of 47) and mean incontinence score (4.9 *versus* 4.2). The fistula healing time and degree of satisfaction with the operation were not significantly different between the groups. One-half of the patients treated by TSSF had the seton removed under general or epidural anaesthesia.

Conclusion Both techniques are equally effective in eradicating the fistula, and both are associated with a similar rate of incontinence.

The majority of anal fistulas are superficial and easily treated by fistulotomy¹. However, because of the risks of incontinence and recurrence, the treatment of high anal fistula remains a significant surgical challenge. Setons are the oldest of the surgical alternatives developed over the years to respond to this challenge².

A seton is a thread of foreign material inserted through the fistulous track. Setons have been used for years with different purposes in anorectal surgery³. Their use in the management of high anal fistula is based on the assumption that they cause a chronic inflammatory reaction and consequent fibrosis that fixes and prevents retraction of the sphincter when it is divided⁴. The cutting seton and the two-stage fistulotomy (TSSF) are the most commonly used techniques based on this simple surgical principle^{5,6}. By periodic tightening around the tissue encircled by the fistula, the cutting seton gradually transects the muscle by pressure necrosis⁵. In the TSSF, the seton is left loose around the tissue encircled by the fistula to stimulate fibrosis. Division of the muscle encircled by the fistula is then performed as a second procedure⁷. Good clinical results have been described with both techniques^{8–19}. Proponents of the cutting seton argue that they do not need a second operation¹³, whereas those in favour of the TSSF argue that the cutting seton produces unnecessary pain and divides the sphincter in an uncontrolled way¹². In this study the clinical results obtained with both seton techniques in the surgical management of high anal fistula are compared.

Patients and methods

The records of 624 patients with anal fistula of cryptoglandular origin treated over a 5-year period were reviewed. Information related to the fistula and its surgical treatment was retrospectively obtained by reviewing charts and operative reports. Information regarding fistula recurrence and postoperative incontinence was investigated by a mailed questionnaire. The response rate was 60 per cent.

Of the 375 patients returning questionnaires 59 (16.5 per cent) had been treated by either cutting seton ($n = 12$) or TSSF ($n = 47$). The operative reports of two patients treated by TSSF did not contain enough information about the type of fistula and the amount of muscle involved by the fistula and therefore were excluded from the study. One patient was treated twice with TSSF.

The operations were performed under general or local anaesthesia with the patient in the prone jack-knife position. The decision to use a seton was made during operation based on the anatomy of the fistula and the relationship of the track with the sphincter mechanism. The portion of the track outside the sphincter mechanism and any lateral secondary tracks were laid open. The granulation tissue was removed from the fistulous track with the help of a curette. The anoderm and perianal skin overlying the portion of the sphincter complex to be divided by the seton were incised, and the intersphincteric space was drained by division of the internal sphincter. A high blind track, when present, was managed by cephalad extension of the internal sphincterotomy. The edges of the anoderm and skin were marsupialized with a 3/0 catgut suture.

For the TSSF a no. 2 silk suture was loosely tied with multiple knots around the remaining muscular portion of the sphincter complex. The seton was left in place for at least 6 weeks. The secondary fistulotomy was done either in outpatients or in the operating room, depending on the amount of muscle to be divided and the tolerance of the patient. For the cutting seton technique a rubber band was passed through the fistulous track and tied loosely around the sphincter mechanism. The tightening

of the rubber band seton was not started until the suppurative process had resolved and the fistulotomy wound was starting to heal. The seton was tightened by applying a silk tie or a 'Barron' ligature to the stretched rubber band²⁰. After the first visit the tightening was repeated every 2 weeks until the seton cut through the muscle.

Any noticeable difficulty in controlling flatus, soiling underwear, or accidental bowel movement that persisted for more than 1 month after the operation was considered as incontinence. Based on the questionnaire answer, a clinical incontinence score scale was created with 0 being perfect continence and 21 representing total incontinence. The results were compared by Student *t* and χ^2 tests as indicated.

Results

This study includes 59 patients with high anal fistula treated by cutting seton ($n=12$) or TSSF ($n=47$). Mean age of the patients was 45 years and was similar for both groups (42 years for cutting seton *versus* 46 years for TSSF). There were more men than women in the TSSF group (27 *versus* 20), while in the cutting seton group there was an identical number of men and women; these differences were not statistically significant. Difference in follow-up (27 months for cutting seton *versus* 33 months for TSSF) were not statistically significant (Table 1).

The fistula was trans-sphincteric in 50 patients (11 cutting seton, 39 TSSF), suprasphincteric in four (one cutting seton, three TSSF) and extrasphincteric in five (all TSSF). The mean amount of external sphincter involved by the fistula as estimated by the operating surgeon at the time of the operation was 54 per cent for the fistulas treated by cutting seton and 57 per cent for those treated by TSSF. These differences were not statistically significant (Table 1).

Fistulas recurred in five patients (8.5 per cent), four treated with TSSF and one with cutting seton (Table 2). All patients with recurrence had previous fistula operations, and in four the fistula had a horseshoe extension. One of the four patients with recurrence after TSSF was treated successfully with the same technique.

Sixty-six per cent of the patients had postoperative change in their continence status. Patients treated by either technique were equally likely to develop postoperative alteration in the continence status (Table 2). The proportion of patients with difficulty holding gas and stool incontinence were similar in both groups (Table 2). Slightly more patients treated by cutting seton than TSSF complained of underwear staining, but the difference did not reach statistical significance (Table 2). The mean incontinence score was not significantly different between groups (Table 2).

The time for the fistula to heal was not significantly different between groups (16.5 weeks for cutting seton *versus* 15.1 weeks for TSSF). Patients treated by cutting seton required a single surgical operation, but 56 per cent of patients treated by TSSF required a second operation under general or epidural anaesthesia.

Degree of satisfaction with the operations was not significantly different between groups ($P=0.767$). Most of them were either 'satisfied' or 'very satisfied' with the procedure (Table 3). Dissatisfaction was associated either with recurrence (three of eight) or high incontinence score (mean 9.6). Eight patients had to wear a pad permanently.

Table 1 Characteristics of 59 patients with high anal fistula treated by cutting seton or two-stage seton fistulotomy

	Cutting seton	TSSF	P
No. of procedures	12	47	
Mean(s.e.) age	41.7(3.1)	45.8(1.9)	0.33*
M:F ratio	6:6	27:20	0.65†
Mean(s.e.) external sphincter involved (%)	54(7.0)	57(4.3)	0.77*
Mean(s.e.) follow-up (months)	27(5.1)	32.6(2.6)	0.34*

* χ^2 test for association with sex; †Student's *t* test for differences in mean. TSSF, two-stage seton fistulotomy

Table 2 Fistula recurrence, incontinence, and healing time in patients with high anal fistula treated by cutting seton and two-stage seton fistulotomy

	Cutting seton ($n=12$)	TSSF ($n=47$)	P*
Recurrence	1	4	0.98
Incontinence	8	31	0.96
Gas	6	25	0.84
Stain	6	18	0.46
Stool	3	12	0.97
Incontinence score	4.9(1.4)	4.2(6.1)	0.62
Healing time (weeks)	16(2.9)	15(2.2)	0.69

Values are mean(s.e.) * χ^2 test for association. TSSF, two stage seton fistulotomy

Table 3 Satisfaction of patients with high anal fistula treated by cutting seton and two-stage seton fistulotomy

Satisfaction*	Cutting seton ($n=12$)	TSSF ($n=47$)
1 Very satisfied	6	19
2 Satisfied	5	21
3 Unsatisfied	1	7
4 Very unsatisfied	0	0

Values are mean(s.e.). * χ^2 test for association with satisfaction. TSSF, two-stage seton fistulotomy

Discussion

A recent review of the literature has confirmed the almost universally accepted observation that seton techniques are successful in the treatment of complex fistula in ano³. However, the selection of the type of seton is based on personal preferences, and the advantages and disadvantages of the different seton techniques have not been clearly established.

Despite the limitation of any retrospective review and the small number of patients in one of the arms, the present study indicates that there are no clinical differences between patients with high anal fistulas treated either by TSSF or cutting seton. Recurrence of fistula, postoperative incontinence, mean incontinence score, healing time, and degree of satisfaction with the procedure were not significantly different between groups. The cutting seton avoids a second operation for one-half of the patients treated by TSSF.

Recurrence of fistula was identical in both groups of patients, and it was similar to the recurrence rate reported in other published series of patients with fistulas treated with setons^{11,15,18}. This was not surprising because the present authors have previously demonstrated that recurrence after surgical treatment for fistula in ano was more dependent on the surgeon performing the operation than on the technique²¹ chosen to treat it.

The most disturbing finding of this study was the significant proportion of patients complaining of permanent postoperative change in their continence. Most of these complaints were minor as reflected by the low mean incontinence score and the degree of patient satisfaction. However, 13 per cent of the patients were dissatisfied with the operation, and the same proportion had to wear a pad permanently.

While some authors have published series of patients with high anal fistulas treated by cutting seton with minimal postoperative change in their continence status^{9,12,16,17,19} others have reported rates of postoperative incontinence similar to the present results among patients with complex anal fistula treated by either TSSF¹⁰ or cutting seton^{11,15}. The present results support the idea that variations in the methodology used to determine the functional outcome, and not the seton techniques, are responsible for the large discrepancy in postoperative incontinence rates reported in different series. A uniform system to report functional outcome after anorectal surgery is clearly required.

In conclusion, the TSSF and the cutting seton are equally effective in eradicating anal fistulas, but both are followed by a significant degree of postoperative incontinence.

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Continued change in the distribution of colorectal carcinoma

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Background The aim of this study was to determine whether the previously reported shift in carcinoma from the left colon to the right colon has progressed.

Methods The charts of 2169 patients admitted to one institution between 1979 and 1994 with a diagnosis of colorectal carcinoma were reviewed retrospectively. The study was divided into four equal intervals. The large bowel was divided into five regions: right, transverse, left, sigmoid and rectum.

Results Right-sided lesions increased from 20.6 to 29.9 per cent ($P = 0.001$) and rectal lesions decreased from 22.0 to 11.3 per cent ($P = 0.0002$) from the first to the fourth study interval. The frequency of transverse, left and sigmoid colon lesions remained relatively constant.

Conclusion The continuing trend of increased incidence of right-sided lesions and decreased incidence of rectal lesions was documented. Any screening examination for carcinoma requires total examination of the colon.

In the 1980s there were many reports that addressed the subject of the changing distribution of colorectal carcinoma. Most reports noted a shift to the right side of the colon. In 1982 Mamazza and Gordon¹ reported on 1044 cases from the Sir Mortimer B. Davis Jewish General Hospital in Montreal, Canada, and noted an increase from 15.6 to 35 per cent in the incidence of right-sided lesions, and a decrease in the incidence of rectal carcinoma from 53 to 2.1 per cent. Follow-up from the same hospital is now reported. Between 1979 and 1994 2169 patients were admitted with the diagnosis of colorectal adenocarcinoma. This report describes the distribution of these carcinomas.

Patients and methods

All patients admitted from 1 April 1979 to 31 December 1994 with diagnosis of adenocarcinoma of the large intestine were included in the review. Patient files were identified by reviewing the medical records database. Names that appeared more than once had chart reviews. Synchronous lesions that occurred in more than one anatomical portion of the intestine were counted as two primaries. Metachronous lesions were identified if they occurred more than 1 year after the original surgery and were not anastomotic in origin. There was a total of 2169 patients with 2195 lesions. Some 107 patients were excluded because it was impossible to determine the site of the lesion.

For analysis, the large bowel was divided into five regions: (1) right colon (including caecum, ascending colon and hepatic flexure); (2) transverse colon; (3) left colon (including splenic flexure and descending colon); (4) sigmoid colon (including rectosigmoid); and (5) rectum. The 16 years studied were divided into four 4-year intervals.

All data were entered on to an IBM-compatible computer using WORKS for Windows database. χ^2 test for trend analysis was performed to indicate the changing frequencies of the five anatomical regions of the large intestine in 4-year groupings. Statistical significance was considered at $P < 0.05$.

Results

Between 1979 and 1994, the number of patients diagnosed with colorectal carcinoma remained constant at this

institution (Table 1). Right-sided colonic cancers steadily increased from 20.6 to 29.9 per cent ($P = 0.001$) over the 16 years analysed (Fig 1). Most of this increase occurred in caecal and ascending colonic carcinomas. Both increased by 50 per cent. Transverse, left and sigmoid colonic carcinomas remained relatively constant. Transverse colonic cancers had a variable incidence, from

Table 1 Changing distribution of colonic and rectal carcinomas of patients admitted between 1979 and 1994

	Right colon	Transverse colon	Left colon	Sigmoid colon	Rectum	Total
1979–1982	103	11	53	195	103	465
1983–1986	129	25	54	254	71	533
1987–1990	131	35	61	207	94	528
1991–1994	169	29	65	216	66	545

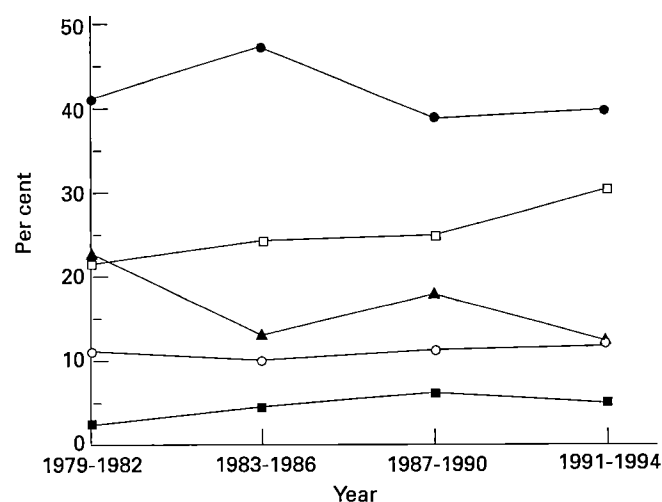


Fig. 1 Proportion of carcinomas in different segments of the large intestine during the years 1979–1994. ●, Sigmoid; □, right colon; ▲, rectum; ○, left colon; ■, transverse colon

3.6 to 5 per cent between the beginning and the end of the study. Left colonic cancers varied between 10.4 and 11.3 per cent and sigmoid carcinomas decreased from 38.4 to 37.7 per cent. Rectal cancers reduced by one-half, from 22.0 per cent for the first 4 years to 11.3 per cent in the last interval analysed ($P = 0.0002$).

Discussion

Before 1985 many authors noted an increasing shift from left-sided to right-sided colorectal cancers²⁻¹⁰ but since then the literature has had few further reports¹¹⁻¹³; not all reports are in agreement¹⁴. Despite the fact that the definitions of proximal and distal lesions are not uniform and the studies are largely retrospective, evidence from hospital-based^{2,4,6,11,14-17}, population-based^{18,19}, regional databases^{3,10,20,21}, tumour-registry investigations^{9,22}, or the Surveillance, Epidemiology and End Results (SEER) Program²³⁻²⁵, suggest that this proximal migration is real.

The present study noted an increase from 24 to 35 per cent in cancers proximal to the splenic flexure and a decrease from 70 to 60 per cent in those distal. Ghahremani and Dowlatshahi²⁶ reviewed 1694 consecutive cases and noted a 10 per cent increase in right-sided lesions and a 15.8 per cent decrease in rectosigmoid cancers. This is in contrast to Crerand *et al.*²⁷ who reported that 75 per cent of 1553 patients had left colonic tumours. Jass²⁸ evaluated 15 395 patients and, when age-adjusted, noted the increase in right colonic cancers was particularly evident in the elderly. There was a marked reduction in incidence of left colonic and rectal carcinoma in individuals under the age of 50 years, but the incidence of right colonic carcinoma appeared relatively stable in this age group. Fleshner *et al.*¹¹ also found the mean age of patients with right colonic cancers to be significantly higher than for patients with left colonic or rectal tumours. In a report by Cady *et al.*¹⁵ the distribution of carcinomas in the large intestine was almost identical to that in this study.

Even though 25 cm of mucosa can theoretically be visualized by rigid sigmoidoscopy, only the distal 16 cm is reliably examined²⁹. Combining the incidence of rectal and rectosigmoid lesions in the present series, a decrease from 40.9 to 25.8 per cent of these lesions was noted over the 16 years. Thus, only 25 per cent of cancers would be detected by rigid sigmoidoscopy. The addition of flexible sigmoidoscopy, which allows 60 cm of distal colon to be evaluated, would increase this yield to about 50 per cent, down from 60 per cent in 1979. Despite the shift to the right, more lesions still occur in the left colon and therefore the flexible sigmoidoscope remains an important diagnostic tool.

This review is institution-based and may not precisely reflect population-based data. Fewer patients with rectal carcinoma may have been referred to this particular hospital, but this is unlikely because of the special interest of this group in sphincter-saving procedures. In addition, the caseload includes the colorectal carcinomas of all surgeons operating at this hospital during this interval and reflects a mix of private practice general surgeons and university-affiliated general and colorectal surgeons. Absolute numbers of cases referred have remained unchanged.

Reasons for this change in distribution are not entirely clear. It may be because of increased detection and removal of rectal polyps³⁰. The frequency of colonoscopy

and flexible sigmoidoscopy has dramatically increased over the study interval and all detected adenomas were removed. This change in practice should equally have decreased the incidence of right-sided colonic cancers, which was not the case. In a necropsy study, Offerhaus *et al.*³¹ noted an increased incidence of adenomas in the right colon and a decreasing incidence of rectal adenomas. Gerharz *et al.*³² noted an age-dependent shift to the right of colorectal adenomas. Therefore, an ageing population may be more prone to the development of right-sided carcinomas. Devesa and Chow in Milne³³, working with SEER tumour registries, confirmed the right shift, but saw the shift more in older populations. Cooper *et al.*¹⁹ conducted a national population-based study of 75 266 Medicare beneficiaries and found the incidence of colorectal carcinoma increased from 1.59 per 1000 in patients aged 65-69 years to 3.87 per 1000 in those aged 85 years or more. The proportion of cancers beyond the reach of the sigmoidoscope increased with age as did the actual incidence of accessible lesions.

Other theories espoused for the change in distribution include changing dietary habits (high fat and low fibre)³⁴. The increased incidence of right-sided carcinomas in patients who have had a cholecystectomy has also been noted by some, but refuted by others^{35,36}. It has been suggested that the geographical location of carcinoma towards the right side is simply a feature of the ageing gut¹⁶.

This study reviewed over 2000 patients with large intestinal carcinoma and noted a continuation of the trend to more right-sided tumours. The shift reported in the present author's previous 24-year study¹ has continued in the current 16-year study. The phenomenon appears real and supports the contention that colonoscopy or other investigations employed must examine the entire colon and not just the distal portion, otherwise over one-half of carcinomas will be missed.

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Quality of life after pouch excision

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Background Pouch excision is a devastating experience for patients having restorative proctocolectomy for ulcerative colitis.

Methods The quality of life among patients having pouch excision for ulcerative colitis was compared with that in those having proctocolectomy and ileostomy for ulcerative colitis using a validated standardized self-administered questionnaire.

Results After pouch excision patients ($n = 9$) had more troublesome bowel symptoms (mainly from liquid stoma output) than those in the proctocolectomy group ($n = 14$) (mean(s.d.) score 5.64(0.92) versus 6.13(0.37), $P = 0.03$). However, the mean scores for the other parameters (systemic symptoms, functional, social and emotional impairment) did not differ significantly.

Conclusion Patients having pouch excision for ulcerative colitis have more liquid ileostomy loss but a comparable quality of life to those treated by standard proctocolectomy and ileostomy.

Pouch excision is the ultimate 'failure' for patients who have had a restorative proctocolectomy for ulcerative colitis, hoping thereby to avoid a permanent ileostomy. Pouch excision usually represents the culmination of a period of long-term postoperative morbidity characterized by pelvic sepsis^{1–3}, chronic pouchitis⁴, debilitating pouch-related fistula⁵ or poor pouch function^{6,7}. Pouch excision may, therefore, be a relief for patients who have had to endure these disabling symptoms even though it involves a permanent stoma. The quality of life of this group of patients was evaluated using a previously validated and standardized self-administered questionnaire which examines systemic and bowel symptoms, functional and social impairment, and emotional function⁸.

Patients and methods

Patients having pouch excision after restorative proctocolectomy for ulcerative colitis were identified from a computerized database for patients with a pouch. A comparative group of patients with ulcerative colitis of similar age and sex treated by standard proctocolectomy and ileostomy over the same interval were selected from the records.

All patients were sent a 36-question questionnaire adapted from that used by Love *et al.*⁹. There were five groups of questions identifiable into five parameters of function: bowel symptoms (eight questions), systemic symptoms (seven), functional impairment (seven), social impairment (six) and emotional impairment (eight). Response to each question was scored on a seven-point scale where 1 represented the worst function and 7 represented the best function. Nine of 11 patients having had a pouch excision with the underlying diagnosis of ulcerative colitis completed and returned the questionnaire, whereas 14 of 17 patients with ulcerative colitis treated over the same time period by standard proctocolectomy (comparator group) completed and returned it.

The results were analysed by comparing the scores globally and for each parameter of function using Students unpaired *t* test.

Function was also compared with the length of bowel removed during pouch excision. Eleven patients having pouch excision who were found to have Crohn's disease were excluded

deliberately, because pouch excision in many of these patients was specifically for Crohn's disease-related complications^{10–12}. Similarly, some patients have had pouch excision with an underlying diagnosis of familial adenomatous polyposis ($n = 1$) or megacolon–constipation ($n = 2$). The reasons for pouch excision in these groups are complex, with a mixture of physical, emotional and functional factors that would distort a true comparison of failed pouches or standard proctocolectomy for ulcerative colitis; hence patients in these groups were also excluded.

Results

Demography

The age, sex and year of operation of patients with an excised pouch were comparable to those in the proctocolectomy group, as outlined in Table 1. However, the amount of small bowel eventually resected differed markedly. Based on pathology reports (corrected +30 per cent for fixed material), the median (range) of small bowel resected was 51 (44–62) cm in excised pouches compared with 6 (4–11) cm in the proctocolectomy group.

Quality of life scores

Mean scores for the five parameters of function and the overall score (sum total of all five dimensions) of patients in the pouch excision group and those in the

Table 1 Demographic findings in patients with ulcerative colitis

	Excised pouch ($n = 9$)	Proctocolectomy ($n = 14$)
Sex ratio (M:F)	4:5	6:8
Median (range) age (years)	41 (13–65)	49.5 (24–74)
Year of operation		
1985–1990	4	6
1990–1995	5	8
Median (range) amount of small bowel excised (cm)	51 (44–62)	6 (4–11)

Table 2 Quality of life scores

Parameter of function	Excised pouch (n = 9)	Proctocolectomy (n = 14)	P*
Bowel symptoms	5.64(0.92)	6.13(0.37)	0.03
Systemic symptoms	5.71(0.83)	6.20(0.36)	0.08
Functional impairment	5.94(0.95)	6.49(0.50)	0.06
Social impairment	5.89(0.74)	6.29(0.45)	0.08
Emotional impairment	6.25(0.71)	6.64(0.35)	0.12
Global score	5.89(0.70)	6.36(0.28)	0.08

Values are mean(s.d.). Score ranged from 1 (poor) to 7 (good).

*Student's unpaired *t* test

proctocolectomy group are outlined in Table 2. Mean scores for bowel and systemic symptoms, and for functional, social and emotional impairment, were all lower in the excised pouch group than in the proctocolectomy group. However, the difference was statistically significant only for bowel symptoms ($P = 0.03$). The particular differences in bowel symptoms included frequency of emptying the ileostomy bag, watery ileostomy output, abdominal cramps, passing large amounts of gas into the bag, abdominal bloating, bleeding into the ileostomy, a feeling of having to empty the bowels and disruption of family life by these bowel symptoms. The other non-bowel parameters such as systemic symptoms (fatigue, lethargy, nausea, weight, etc.), functional impairment (work, leisure, sports, sleep, etc.), social impairment (engagements, sexual function, leakage or noises causing embarrassment, etc.), and emotional impairment (frustration, fear, depression, anxiety, anger, etc.) did not differ significantly between the groups.

Quality of life scores and length of bowel excised

The length of bowel excised in the excised pouch group was recorded from the pathology reports (corrected for fixed material + 30 per cent) and operation records. The length varied from 44 to 62 cm: four patients lost less than 50 cm, three lost between 50 and 60 cm and the remaining two lost more than 60 cm. There was no correlation between the amount of bowel excised and bowel symptoms score. However, the frequency of emptying bags and watery stoma output were probably due to the loss of terminal ileum in the excised pouch group.

Discussion

Restorative proctocolectomy is now regarded as the established procedure³ for patients with ulcerative colitis who require colectomy. Restorative proctocolectomy is considered¹³ by most clinicians to be preferable to standard proctocolectomy and ileostomy as it spares patients the morbidity associated with an ileostomy and quality of life is universally superior^{14,15}. However, complications or poor function following restorative proctocolectomy have resulted in 6–22 per cent^{1–3,16,17} of patients requiring pouch excision and an ileostomy. The aim of the present study was to determine whether patients who lose their pouch have a quality of life that is comparable with that of patients who decide not to risk these complications and accept a permanent ileostomy from the beginning. Health-related quality of life assessment^{8,18–21} is a quantitative measure of a patient's subjective evaluation of their perceptions, illness experience, and functional, social and emotional states. The problem with any

evaluation of quality of life is the lack of a universally acceptable index of measurement. The use of a standardized quality of life questionnaire is of great value for comparing patients receiving different forms of therapy. It was decided to adopt the questionnaire used by Love *et al.*⁹ for those with inflammatory bowel disease, but to adapt it for patients with an ileostomy. A deliberate attempt was made to avoid comparing quality of life with a group whose sphincter had been preserved, as bowel assessment would be bound to differ.

Results showed overall that patients with an excised pouch have a comparable quality of life to those who chose to have conventional proctocolectomy and ileostomy. However, patients who undergo pouch excision have more troublesome bowel symptoms than those who have conventional proctocolectomy. This is explained by the shorter length of remaining small bowel after pouch excision resulting in an increased frequency of emptying the ileostomy bag, more watery ileostomy output and a greater frequency of abdominal cramps and bloating. However, bowel symptoms did not correlate with the length of bowel excised, probably because the length of excised bowel did not differ greatly in the nine patients whose pouch was removed for ulcerative colitis. By contrast, when the diagnosis was Crohn's disease the length of bowel excised varied from 48 to 108 cm. However, pouch excision did not significantly affect the other aspects of quality of life. For instance, these bowel disturbances did not increase the incidence of systemic symptoms or produce more functional and social impairment than conventional proctocolectomy.

However, these data are based on relatively small numbers as the authors wished to confine pouch excision to patients with proven ulcerative colitis and many patients were found to have Crohn's disease¹¹. It is conceivable that a larger sample size might have exposed a real difference between the groups. Despite this, it is encouraging to find that failed pouch surgery for ulcerative colitis does not appear to be as great a disaster as might be presumed. Indeed, apart from increased ileostomy fluid loss, the functional, emotional and social results are almost identical to those recorded from patients treated by conventional proctocolectomy and ileostomy.

These results indicate that patients with an excised pouch are not greatly disadvantaged compared with those who decide not to risk the potential complications and uncertainty of an ileoanal pouch in the first place. Patients who have pouch excision do suffer from increased bowel symptoms and the potential metabolic sequelae of ileal resection, notably vitamin B₁₂ deficiency^{22–24}, but pouch excision does not appear to affect the other aspects of their lifestyle, which is comparable to that of those who decide from the outset to have a standard proctocolectomy.

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Pattern of lymph node metastases in papillary thyroid carcinoma

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Background Incidence and pattern of lymph node metastasis (LNM) were evaluated in 35 patients who underwent primary surgery for papillary thyroid carcinoma.

Methods Total thyroidectomy with systematic cervicocentral lymphadenectomy was performed routinely. Additionally, 22 patients underwent lymphadenectomy of the ipsilateral cervicolateral compartment. Sternotomy was performed in four patients.

Results Primary tumour status was: pT₁, *n* = 7; pT₂, *n* = 12; pT₃, *n* = 4; pT₄, *n* = 12. Twenty-four patients had LNM in the ipsilateral cervicocentral compartment (pT₁, *n* = 2; pT₂, *n* = 8; pT₃, *n* = 4; pT₄, *n* = 10). Nineteen had LNM in the ipsilateral cervicolateral compartment (pT₁, *n* = 4; pT₂, *n* = 6; pT₃, *n* = 2; pT₄, *n* = 7). Contralateral cervicocentral LNM was restricted to patients with pT₃ tumours (*n* = 2) or pT₄ tumours (*n* = 3). No patient had LNM in the contralateral cervicolateral compartment. Only one patient (pT₃ tumour) had mediastinal LNM.

Conclusion The cervicocentral compartment was most commonly involved with metastases, although the ipsilateral cervicolateral compartment was almost as often affected. In some patients ipsilateral cervicolateral LNM was present in the absence of cervicocentral LNM. Contralateral cervicolateral and upper mediastinal LNM, however, were rare. This study helps to plan radical surgery for papillary thyroid carcinoma.

Because of the prolonged course of papillary thyroid carcinoma (PTC) the extent of surgical treatment continues to be the subject of controversy. Various aspects of surgical treatment have been debated: whether or not total thyroidectomy is required in all cases^{1–4} and to what extent lymph nodes should be removed. The extent of lymph node dissection depends on whether lymph node metastasis (LNM) influences recurrence and survival, the pattern of LNM and whether lymphadenectomy can improve outcome.

Many studies with short follow-up do not report a significant influence of LNM on outcome. In a meta-analysis of 16 studies Goretzki *et al.*⁵ did not find any prognostic significance of LNM regarding survival. In contrast, two studies with a mean follow-up of more than 15 years identified a significant adverse influence of LNM^{6,7}. A univariate and multivariate analysis of 342 patients with PTC, with a mean follow-up of 11.8 years from this institution showed a significant influence of LNM concerning recurrence and survival⁸. McHenry *et al.*⁹ also found that LNM is associated with a higher incidence of recurrence and an increased development of distant metastasis, and therefore recommended modified neck dissection.

Few authors have analysed the pattern of metastasis in PTC^{10,11}. The lack of a lymph node compartment definition has previously hindered this analysis. The present authors¹² compared their previously described compartment definition¹³ with the new classification of the Union International Contra la Cancerum (UICC)¹⁴.

In the present study 35 patients, primarily operated on for PTC, were studied to describe the pattern of LNM. The aim was to determine the necessary extent of lymphadenectomy for PTC.

Patients and methods

Thirty-five consecutive patients with PTC proven before operation (dissected cervical lymph node, 11; fine-needle aspiration cytology, 19), or during operation (frozen section, five) had primary surgery in this department. Computed tomography (CT) or magnetic resonance imaging (MRI) were performed when extrathyroid tumour, retrosternal extension or multiple cervical LNM were suspected. All patients had total thyroidectomy as well as systematic lymphadenectomy of the cervicocentral compartment (C1). In those with LNM of the cervicolateral (C2 or C3) or upper mediastinal compartment (C4), diagnosed before operation (clinically, three; ultrasonography, ten; CT and MRI, seven) or during operation, systematic lymphadenectomy of the involved compartment was performed.

Compartment definition of cervicomediastinal lymph nodes

To analyse the pattern of LNM the following definition of four regional lymph node compartments was used¹⁵.

Compartment C1, cervicocentral lymph node system, right (C1a) and left (C1b) from the trachea, between trachea and carotid sheath, and from the hyoid bone down to the brachiocephalic vein including the submandibular lymph nodes.

Compartment C2 (right) and C3 (left) cervicolateral lymph node system between the carotid sheath and trapezoid muscle, from the subclavian vein up to the hypoglossal nerve, anterior, posterior, and between the fascicles of cervical plexus.

Compartment C4, mediastinal lymph node system on both sides of the trachea (right (C4a) and left (C4b)), from the innominate artery and brachiocephalic vein down to the tracheal bifurcation within the anterior and posterior part of the mediastinum.

Technique of systematic, compartment-oriented microdissection of cervicomediastinal lymph nodes

In contrast to selective lymphadenectomy, i.e. removal of macroscopically involved lymph nodes, with or without interstitial adipose tissue, the principle of systematic, compartment-oriented microdissection is the anatomic *en bloc* microdissection of locoregional compartments with the enclosed lymph nodes,

adipose, and connective tissue using magnifying glasses and bipolar coagulation forceps. The sternomastoid muscle, internal jugular vein, transverse cervical artery, thoracic duct, accessory nerve, brachial plexus, sympathetic trunk, and phrenic nerve are identified and preserved.

The *en bloc* excised compartments were carefully analysed to determine the number of dissected lymph nodes as well as tumour involvement. Lymph nodes were separated from adipose tissue and cut through to the nodal hilum to expose the maximum surface area. Size of metastases was defined as the maximum diameter of the metastatic focus within the lymph node.

Results

Mean age at diagnosis of the 26 women and nine men with PTC was 47 (range 15–82) years. The primary tumour status analysed according to UICC was seven for pT₁, 12 for pT₂, four for pT₃, and 12 for pT₄. In eight patients both thyroid lobes were involved, tumour was restricted to the right lobe in 13 and to the left lobe in 14.

LNM was found in 29 patients (Table 1). Twenty-four involved the cervicocentral compartment (C1), 11 the right cervicolateral compartment (C2), and eight the left cervicolateral compartment (C3). Mediastinal lymph node involvement (C4) was found in only one patient (pT₃

tumour). Mean number of lymph nodes dissected from both paratracheal cervicocentral compartment (C1a, 4.6; C1b, 4.3) as well as the number of involved lymph nodes (C1a, 1.6; C1b, 1.9) was similar. Mean number of lymph nodes dissected from both cervicolateral compartments (C2, 21.0; C3, 21.9) was also similar. The number of involved lymph nodes was slightly higher on the left than on the right (C2, 2.0; C3, 4.3) (*P* not significant).

Relation between primary tumour and lymph node metastases

The histological results and pattern of LNM according to pT category are shown in Table 1.

Thirteen of 21 patients in whom the right thyroid lobe was affected had LNM in the right cervicocentral compartment (C1a) and 14 of 22 patients in whom the left thyroid lobe was involved had LNM in the left cervicocentral compartment (C1b). Contralateral cervicocentral spread was identified in only five patients (Table 1), two with a pT₃ tumour and three with a unilateral multifocal pT₄ tumour. Ipsilateral cervicocentral LNM was present in all five patients.

In 19 patients ipsilateral cervicolateral LNM was found. In five ipsilateral cervicolateral LNM was dissected in the absence of cervicocentral LNM, but contralateral cervicolateral LNM was never found. Five patients had a unilateral multifocal tumour, all had LNM. Three of these had bilateral cervicocentral LNM, and four had LNM in the ipsilateral cervicolateral compartment.

Eight patients had a bilateral multifocal tumour, all had LNM. Four had bilateral cervicocentral LNM, and five had LNM in the ipsilateral cervicolateral compartment.

Mean diameter of the largest primary tumour was 2.6 (range 0.1–5.0) cm. Fig. 1 shows the percentage of tumour-involved lymph nodes (defined as the number of tumour-involved lymph nodes divided by number of dissected lymph nodes) compared with the diameter of the primary tumour. The larger the primary tumour the higher the percentage of involved lymph nodes ($r=0.61$, $P<0.05$).

Mean diameter of the largest lymph node metastasis was 1.6 (range 0.3–3.0) cm. Size of the metastasis correlated with a higher percentage of tumour-involved lymph nodes ($r=0.26$) but this correlation was not statistically significant.

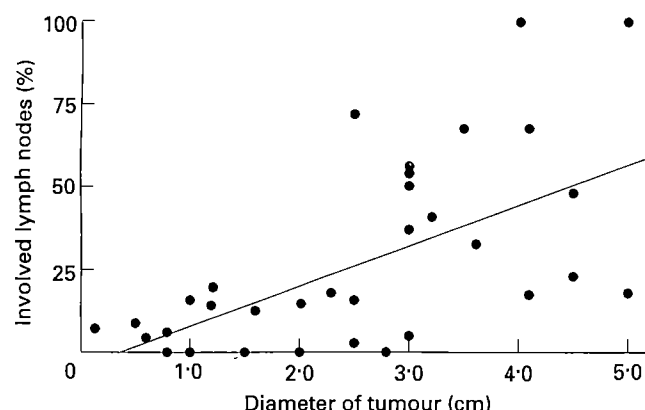


Fig. 1 Percentage of involved lymph nodes (number of tumour-involved lymph nodes divided by number of dissected lymph nodes) related to the diameter of the primary tumour ($n=35$, $r=0.61$, $P<0.05$)

Table 1 Location of lymph node metastasis

	pT ₁ (n = 7)	pT ₂ (n = 12)	pT ₃ (n = 4)	pT ₄ (n = 12)
Lymph node metastases	5	9	4	11
Ipsilateral cervicocentral	1	3	1	4
Ipsilateral cervicolateral	3	1	0	1
Ipsilateral cervicocentral + ipsilateral cervicolateral	1	5	1	3
Ipsilateral cervicocentral + contralateral cervicocentral	0	0	1	0
Ipsilateral cervicocentral + contralateral cervicocentral + ipsilateral cervicolateral + ipsilateral mediastinal	0	0	1	0
Ipsilateral cervicocentral + contralateral cervicocentral + ipsilateral cervicolateral	0	0	0	3
No lymph node involvement	2	3	0	1

Six months after primary operation five patients still required calcium supplements and two had a unilateral paresis of the recurrent laryngeal nerve (mean follow-up 5.9 (range 1–10) years).

Discussion

LNM is commonly found at operation for papillary thyroid cancer but the exact incidence depends on patient selection, the extent of surgery and technique of lymph node dissection. Therefore, metastasis has been reported to be present in 38–90 per cent^{11,15}. Assuming that the presence of LNM in PTC is of prognostic value^{6–8} and that systematic lymphadenectomy might improve survival⁸ it is important to know the pattern of LNM to determine the extent of surgical therapy.

In this series LNM was found in 29 patients with PTC including all patients with a multifocal tumour ($n=13$). LNM was found most often in the cervicocentral compartment ($n=24$), but was present in the ipsilateral cervicolateral compartment in 19 patients. Interestingly, ipsilateral cervicolateral LNM without ipsilateral cervicocentral LNM was found ($n=5$), even in patients with a pT₁ tumour. Therefore, ipsilateral cervicolateral metastatic spread cannot be excluded even if no LNM is found in the cervicocentral compartment (C1). In contrast, contralateral cervicolateral and upper mediastinal LNM are very rare in PTC. Despite the different lymph node compartment classification used in this study these results are in agreement with Noguchi *et al.*¹¹ who found that PTC metastasizes first to the paratracheal nodes.

The percentage of involved lymph nodes increased with higher pT category, but the incidence of LNM did not differ significantly between pT categories (Table 1). Therefore, the surgical approach should be independent of pT category. The only exception might be unifocal pT₁ PTC diagnosed after operation without suspicious lymph nodes. In these patients no additional therapy seems justified.

The present authors have shown a significant prognostic influence of LNM in PTC⁸ and early results suggest that systematic lymphadenectomy may improve survival⁸. It is suggested that total thyroidectomy and, at least cervicocentral systematic lymphadenectomy, should be the treatment for all PTC diagnosed before or during operation. Postoperative radioiodine may fail in the treatment of small metastases¹⁶. Intraoperative detection of this metastases is impossible, therefore systematic lymphadenectomy is recommended instead of selective lymphadenectomy despite a higher morbidity. Further long-term studies will be necessary to justify this approach.

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Prognostic factors in a series of 297 patients with gastric adenocarcinoma undergoing surgical resection

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Background Gastric cancer has a poor prognosis. The aim of this study was to determine the influence of several clinicopathological variables on outcome in a series of 297 Western patients undergoing surgical resection for gastric adenocarcinoma.

Methods The results were analysed retrospectively and prognostic factors were identified in a univariate and Cox proportional hazards regression model. Mean patient age at the time of operation was 61.9 years; 65.7 per cent were men. Mean follow-up was 7.8 (range 1–15) years. Of the 297 patients undergoing surgery, 70 per cent had subtotal gastrectomy, 26.3 per cent underwent total gastrectomy and 3.7 per cent had proximal gastrectomy.

Results The overall survival rate was 38.9 per cent at 5 years. In the univariate analysis, survival-related factors were weight loss ($P < 0.05$), abdominal mass ($P < 0.01$), dysphagia ($P < 0.001$), type of gastrectomy (subtotal gastrectomy *versus* total gastrectomy, $P < 0.001$), intention of resection (curative *versus* palliative resection, $P < 0.001$), tumour site ($P < 0.001$), histopathological grade (low *versus* high grade, $P < 0.05$), tumour diameter less than 3 cm ($P < 0.001$), degree of gastric wall invasion ($P < 0.001$), degree of lymph node invasion ($P < 0.001$) and stage of the neoplasia ($P < 0.001$). Other variables had no significant influence. In the multivariate analysis, degree of gastric wall invasion, lymph node invasion, tumour size and dysphagia at presentation were the only independent prognostic variables.

Conclusion From these data it was possible to derive a prognostic index with which patients could be classified as at low, intermediate or high risk.

Gastric cancer is one of the major causes of cancer-related death in the world, even though its incidence has decreased over the past decade¹. The prognosis is generally poor, especially in Western countries^{2,3} where the overall survival rate at 5 years has not changed, oscillating between 8 and 26 per cent, even though the resectability rate has increased (currently 60–80 per cent) and the postoperative mortality rate has dropped from 14 to 6 per cent^{4–8}. The poor survival is related to delayed diagnosis and frequent local and regional recurrence. Several variables representing pathological, clinical and therapeutic characteristics have already been studied in numerous retrospective reports^{9–15} in an attempt to identify prognostic indicators in patients with gastric cancer and, recently¹⁶, to help define high-risk patients who may benefit from adjuvant therapy.

The aim of this paper was to determine the influence of several clinicopathological variables on outcome in a series of 297 patients undergoing surgical resection for gastric adenocarcinoma. The results were analysed retrospectively and prognostic factors were identified in a univariate and Cox proportional hazards regression model.

Patients and methods

Between January 1979 and December 1994, 321 patients with gastric adenocarcinoma (excluding patients with cancer of the gastric cardia) underwent surgical resection. Excluding 24

operative deaths (defined as those occurring within 30 days of operation), the remaining 297 patients were discharged from hospital and are the subject of study. Mean follow-up was 7.8 (range 1–15) years. Mean patient age at the time of operation was 61.9 (range 30–88) years; 195 patients were men (65.7 per cent) and 102 women (34.3 per cent). Of the 297 patients undergoing surgery, 208 (70.0 per cent) had subtotal gastrectomy, 78 (26.3 per cent) underwent total gastrectomy and the remaining 11 (3.7 per cent) had proximal gastrectomy.

Three types of variable were analysed in the survival analysis. (1) clinical variables including sex, age, evolution time (time elapsed from the appearance of the first symptoms to the time of treatment) and the presence or absence of more meaningful clinical data (epigastric pain, pyloric obstruction, gastrointestinal haemorrhage, weight loss, dysphagia and a palpable abdominal mass), (2) treatment-related variables including the type of operation performed and the intention of the resection – curative (all gross disease is removed at operation) or palliative (gross disease remaining at the conclusion of the operation); and (3) anatomicopathological variables including tumour location, size, tumour structure (exophytic *versus* non-exophytic), degree of tumour differentiation, extent of the disease (tumour confined to the gastric wall *versus* invading adjacent organs or distant metastasis) and tumour node metastasis (TNM) stage (Union Internacional Contra la Cáncer classification¹⁷).

Deaths from causes other than gastric cancer were treated as censored data at the time of death. The survival data are expressed as 5-year survival rates with 95 per cent confidence intervals (c.i.). Survival rates in the different groups were calculated with the Kaplan–Meier estimation method, and survival curves were compared with the log rank test or with its version for testing trends if the categories of the grouping variable were ordered¹⁸.

The possible prognostic factors were evaluated with the Cox proportional hazards regression model¹⁹ by means of a backward

stepwise selection procedure using, in the initial model, variables that were related significantly to survival. Previously, the proportionality assumption was checked for every factor and a violation of this assumption was detected for metastasis. Therefore, this factor was not included in the Cox model and the data were analysed using stratification by metastasis²⁰. The results of significant prognostic factors are expressed as the hazard ratio for each category and its 95 per cent c.i.

Finally, a prognostic index was derived which gave a score to each category of every prognostic factor and used the exponential part of Cox's model with the rounded values of the regression coefficients. Three risk score groups with their survival curves are presented¹⁸.

Results

The overall survival rate in this series was 38.9 per cent at 5 years.

In the univariate analysis (Table 1), the significant factors related to overall survival were: (1) weight loss; (2) abdominal mass; (3) dysphagia; (4) tumour location; (5) histopathological grade; (6) tumour size (Fig. 1); (7) type of surgery – the survival rate of patients undergoing subtotal gastrectomy was 48.1 per cent, compared with 18 per cent after total gastrectomy and 14 per cent after proximal gastrectomy; these differences were statistically significant ($P < 0.001$); (8) intention of the resection – the survival rate of patients undergoing curative resection was 52.5 per cent compared with 7 per cent after palliative resection ($P < 0.001$); (9) penetration depth of the gastric wall (Fig. 2); (10) lymph node involvement – patients without lymphatic invasion (N_0) had a survival rate at 5 years of 69.4 per cent, compared with 35 per cent for those with lymphatic metastasis less than 3 cm from the tumour (N_1) and 10.7 per cent when the metastasis was more than 3 cm away (N_2) ($P < 0.001$) (Fig. 3); (11) stage (Fig. 4). None of the remaining variables studied was significant.

In the multivariate analysis using the Cox model (Table 2) only four variables had a significant association with survival: penetration depth of the gastric wall, lymph node involvement, tumour size and dysphagia at presentation. According to these findings, a prognostic index was obtained which gave a score to each category of every prognostic factor and which used the exponential part of the Cox model with the rounded values, multiplied by 10, of the regression coefficients¹⁸:

Prognostic index:

$$6 \cdot \text{Dysphagia} + 2 \cdot \text{Tumour size} + 7 \cdot T + 4 \cdot N$$

Patients with a maximum of 24 points were classified as at low risk (77 of 297 patients) with a 5-year survival rate of 87 per cent; 27–39 points represented an intermediate risk (169 of 297 patients) with a 5-year survival rate of 33.5 per cent; and those with more than 39 points represented a high risk (51 of 297 patients) with a 5-year survival rate of 0 per cent ($P < 0.001$) (Fig. 5).

Discussion

Prognostic factors in gastric cancer are a source of controversy in many series^{4,6,8,10,12,15}. The aim of the present study was to identify several clinicopathological variables that influence the prognosis of patients with gastric adenocarcinoma after surgical resection. Some authors^{21–23} consider that age *per se* has prognostic value because young patients with gastric cancer have a poorer

prognosis than older patients. Perhaps they present with more advanced disease because the index of suspicion for malignant disease is low and so symptoms are allowed to progress for a longer period before investigation is considered, or there may be greater biological activity of the tumour which is more likely to be of the Laurén diffuse type. Other studies²⁴ have shown that age and sex have a significant influence on outcome. In this study, age and sex did not influence long-term survival.

If, in certain series²⁵, the time between appearance of the first symptoms and treatment is analysed, a poorer prognosis is seen in patients with a short duration (usually less than 6 months). However, other authors²⁶ have reported that prognosis is worse in patients with a long evolution. Another study²⁷ showed no relation between duration of symptoms and prognosis when considered alone, but in combination with tumour diameter duration of symptoms had a prognostic significance in patients undergoing resection. The reason for this relation is thought to be that patients with long-standing symptoms have slow-growing tumours, or gastric 'ulcer-cancers'. Other studies^{11,28} have failed to show any relationship between symptom duration and prognosis. The present study revealed no differences in survival with regard to the preoperative duration of symptoms. However, patients with weight loss, dysphagia or abdominal mass had a worse prognosis, and multivariate analysis showed dysphagia to be an independent factor.

Several authors^{5,7,9,10,15,26,28} have suggested that the more proximal the tumour the worse the survival rate, a situation that has remained unchanged over the past 35 years. In the present series, tumours located in the antrum had a better prognosis, perhaps because the early symptoms caused by pyloric obstruction led to earlier diagnosis.

As far as size is concerned, multivariate analysis failed to show tumour size to be an independent prognostic variable, and it seems unlikely that size has any bearing on survival as an independent factor¹⁰. However, some reports²⁸ have suggested that patients with smaller tumours have a superior prognosis. In this analysis tumours less than 3 cm in diameter had a better prognosis and, in addition, tumour size was an independent prognostic variable of survival. On inter-relating survival with macroscopic type, as in other series^{9,10}, better survival was observed for patients with ulcerated tumours. Perhaps this improved prognosis was found because symptoms such as pain and haemorrhage appear earlier with these tumours. With respect to the degree of cellular differentiation, the best prognosis has been found in well differentiated tumours^{7,9,15,21}. Patients with low-grade tumours had a greater survival rate than those with high-grade tumours, the difference being statistically significant.

In this and other studies^{10,11,14,15,25,29}, the deeper the invasion of the gastric wall the poorer the prognosis. Kaibara *et al.*³⁰ suggested that there are differences in survival depending on the serosal area involved, a smaller affected surface being associated with longer survival. The presence of metastatic tumour in the regional lymph nodes has a highly significant effect on prognosis^{11,22,25,31–34}. Approximately 40 per cent of all node-negative patients are alive at 5 years, compared with 10 per cent of those with lymph node involvement. In this series, the 5-year survival rate of patients without positive lymph nodes was 69.4 per cent *versus* 35 per cent when there was lymphatic involvement. Furthermore, analysis of the degree of lymphatic invasion as proposed by the TNM classification revealed a significantly longer survival in patients with N_1

Table 1 Results of the univariate analysis

Variable	No. of patients*	5-year survival rate (%)†	P‡
Overall	297	38.9 (29–43)	
Sex			
M	194 (65.3)	40.2 (28–55)	n.s.
F	103 (34.7)	36.0 (24–50)	
Age (years)			
< 41	19 (6.4)	41 (16–63)	n.s.
41–69	190 (64.0)	40.2 (29–56)	
> 69	88 (29.6)	35 (20–43)	
Gastrointestinal haemorrhage			
Yes	78 (26.3)	43 (30–57)	n.s.
No	219 (73.7)	37.3 (24–41)	
Pyloric obstruction			
Yes	22 (7.4)	24 (14–41)	n.s.
No	275 (92.6)	40.0 (30–45)	
Weight loss			
Yes	138 (46.5)	31.0 (19–37)	< 0.05
No	159 (53.5)	45.2 (30–67)	
Epigastric pain			
Yes	201 (67.7)	38.2 (30–45)	n.s.
No	96 (32.3)	40 (18–73)	
Abdominal mass			
Yes	26 (8.8)	20 (10–33)	< 0.01
No	271 (91.2)	40.5 (30–50)	
Dysphagia			
Yes	17 (5.7)	6 (2–14)	< 0.001
No	280 (94.3)	41.3 (34–47)	
Duration of symptoms (months)			
< 2	87 (29.3)	42 (14–56)	n.s.
2–6	151 (50.8)	35.6 (16–42)	
> 6	59 (19.9)	29 (24–36)	
Type of gastrectomy			
Proximal	11 (3.7)	14 (8–60)	< 0.001
Subtotal	208 (70.0)	48.1 (36–82)	
Total	78 (26.3)	18 (13–24)	
Type of resection			
Palliative	90 (30.3)	7 (3–14)	< 0.001
Curative	207 (69.7)	52.5 (44–60)	
Splenectomy			
Yes	100 (33.7)	32.7 (18–36)	n.s.
No	197 (66.3)	41.8 (30–66)	
Pancreatectomy			
Yes	17 (5.7)	22 (7–55)	n.s.
No	280 (94.3)	32.1 (24–43)	
Tumour site			
Proximal third	32 (10.8)	17 (12–31)	< 0.001
Mid-stomach	104 (35)	48 (30–47)	
Lower third	161 (54.2)	44.6 (32–70)	
Macroscopic type			
Diffuse	32 (10.8)	12 (8–18)	n.s.
Polypoid	96 (32.3)	30 (20–40)	
Other	169 (56.9)	42.3 (29–60)	
Histopathological grade			
Low	127 (42.8)	45.0 (31–82)	< 0.05
High	170 (57.2)	33.4 (21–39)	
Tumour size (cm)			
< 3	68 (22.9)	71 (58–73)	< 0.001
3–5	96 (32.3)	41 (26–64)	
> 5	133 (44.8)	22.7 (16–26)	
Tumour stage			
T _{is}	19 (6.4)	93 (79–100)	< 0.001
T ₁	27 (9.1)	91 (75–100)	
T ₂	29 (9.8)	65 (56–87)	
T ₃	172 (57.9)	28.8 (20–33)	
T ₄	50 (16.8)	0 (8–18)	
Node stage			
N ₀	108 (36.4)	69.4 (59–79)	< 0.001
N ₁	79 (26.6)	35 (25–39)	
N ₂	110 (37.04)	10.7 (13–18)	
Stage			
0	19 (6.4)	93 (79–100)	< 0.001
I	44 (14.8)	85 (75–100)	
II	51 (17.2)	52 (35–68)	
III	132 (44.4)	23.2 (18–30)	
IV	51 (17.2)	0 (8–15)	

Values in parentheses are *percentages and †95 per cent confidence intervals ‡log rank test

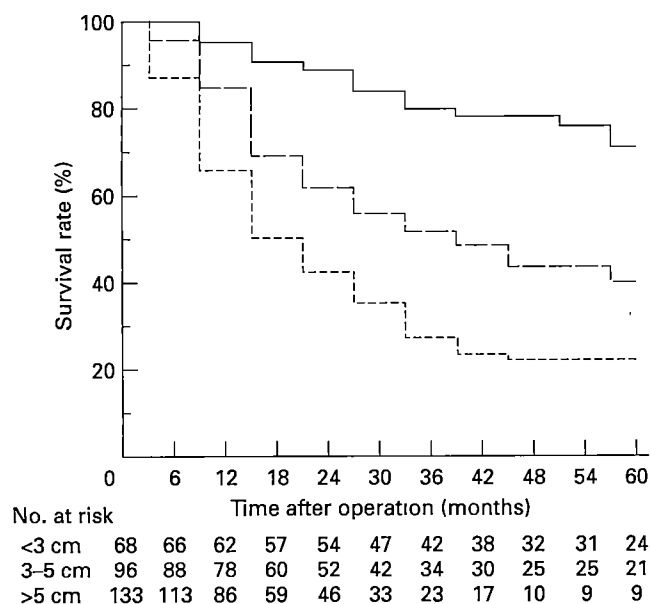


Fig. 1 Kaplan-Meier survival curves according to tumour size: —, diameter less than 3 cm; ---, diameter 3-5 cm; ···, diameter greater than 5 cm. $P < 0.001$ (log rank test)

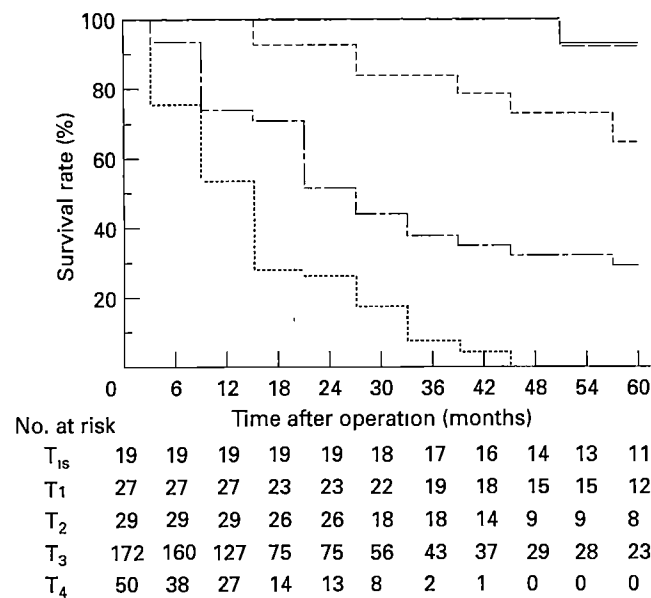


Fig. 2 Kaplan-Meier survival curves according to depth of gastric infiltration (T): —, T_{is}; ---, T₁; ···, T₂; - · - ·, T₃; — · — ·, T₄. $P < 0.001$ (log rank test)

disease. Multivariate statistical analyses all show tumour stage to be the single most important prognostic determinant^{10,12,25,31}. The present data show that the variable with the greatest influence on prognosis is stage, as patients with stage I and II disease had significantly longer survival than those with stages III and IV. However, with Cox's model, stage was not an independent factor although its components (T, N and M) were considered: two in Cox's model (T and N) and the third in the stratification analysis (M). A steady increase in tumour resectability rate has frequently been reported^{2-6,8,13,24,28}. Gall and Hermanek³⁵

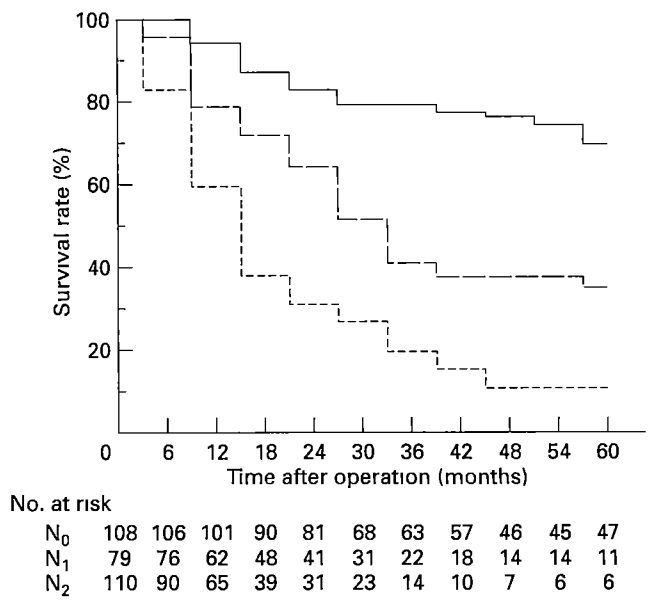


Fig. 3 Kaplan-Meier survival curves according to lymph node involvement (N): —, N₀; ---, N₁; ···, N₂. $P < 0.001$ (log rank test)

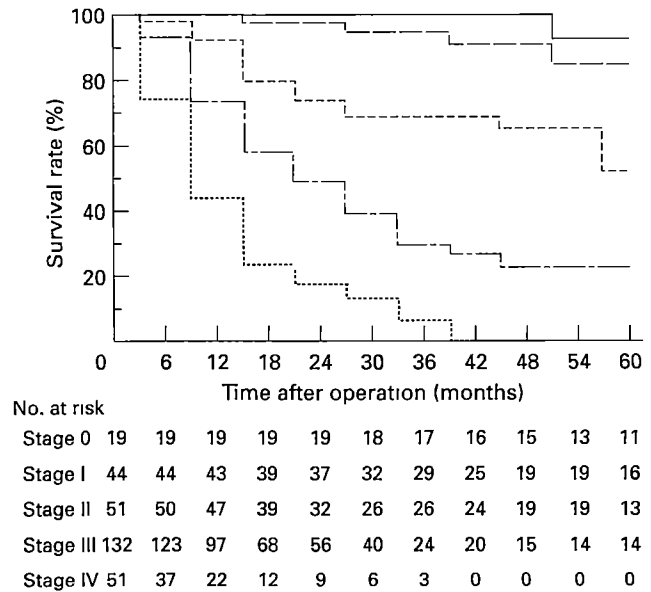


Fig. 4 Kaplan-Meier survival curves according to stage. —, stage 0; ---, stage I; ···, stage II; - · - ·, stage III; — · — ·, stage IV. $P < 0.001$ (log rank test)

reported an increase from 60.8 to 75.9 per cent over two consecutive 5-year periods, which was due mainly to an increase in the number of non-curative resections. There is no doubt that if a tumour is resectable the prognosis is considerably better than when the lesion is irresectable, although prognosis is clearly stage dependent rather than the operation being a prognostic indicator *per se*^{2,4}. Although treatment cannot be considered an independent factor, it can determine the therapeutic attitude. Some surgeons achieve greater survival if they perform total gastrectomy from the outset. On the other hand, others have had better results with subtotal than with total gastrectomy from the outset, as with multivariate analysis

Table 2 Results of survival analysis with Cox's proportional hazards regression model

Variable	Score	Regression coefficient β	Standard error of β	Hazard ratio	P
Dysphagia					
No	0	0	—	1	
Yes	1	0.6394	0.2913	1.8953 (1.0708–3.3547)	0.0282
Tumour size (cm)					
<3	1	0	—	1	
3–5	2	0.2331	0.1278	1.2625 (0.9828–1.6219)	0.0682
>5	3	0.4662		1.5939 (1.2407–2.0476)	0.0003
Depth of gastric infiltration (T)					
T _{is}	0	0	—	1	
T ₁	1	0.6935	0.1329	2.0007 (1.5419–2.596)	<0.0001
T ₂	2	1.387		4.002 (3.0849–5.1939)	<0.0001
T ₃	3	2.0805		8.0085 (6.172–10.3915)	<0.0001
T ₄	4	2.774		16.0226 (12.3483–20.7902)	<0.0001
Lymph node involvement (N)					
N ₀	0	0	—	1	
N ₁	1	0.4327	0.119	1.5414 (1.2207–1.9463)	0.0003
N ₂	2	0.8654		2.376 (1.8817–3.001)	<0.0001

Values in parentheses are 95 per cent confidence intervals

the poor results for total gastrectomy are independent of the degree of neoplasia. Finally, some have found no differences between the two resection techniques. In this study, patients undergoing subtotal gastrectomy had a significantly greater survival rate (48.1 per cent) than those having total gastrectomy (18 per cent) ($P < 0.001$). These differences are due to the fact that total gastrectomy was performed only when necessary, i.e. only in cases in which subtotal gastrectomy could not be performed because of the size or location of the tumour. Although it has been stated that the association of splenectomy diminishes the survival rate^{8,10}, this was not confirmed in the present study.

In conclusion, this retrospective study has shown that degree of gastric wall invasion, lymph node invasion, tumour size and dysphagia at presentation are the only

independent prognostic variables. These findings have enabled the elaboration of a prognostic index with which patients can be classified as at low, intermediate or high risk.

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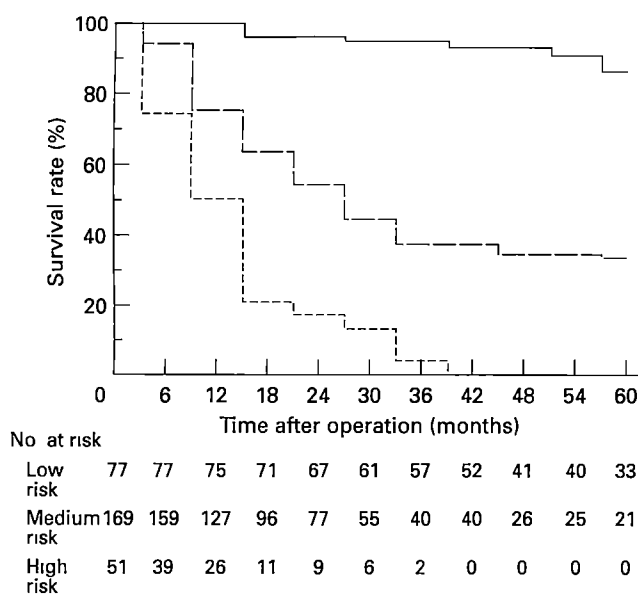


Fig. 5 Kaplan-Meier survival curves according to risk group: —, low risk; ---, medium risk; ···, high risk. $P < 0.001$ (log rank test)

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Restenting malignant oesophageal strictures

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Background Self-expanding metal stents are used to palliate malignant strictures of the oesophagus. This study was designed to identify the characteristics of patients requiring restenting of malignant oesophageal strictures.

Methods Fifty-three stents were inserted in 42 patients. Thirty-two patients did not require further stenting (once-stented group). Ten patients received second stents for recurrent oesophageal obstruction (restented group), with one patient requiring restenting a second time. Comparisons were drawn between the once-stented and restented groups with regard to survival, patient, tumour and procedural characteristics.

Results There were no significant differences with regard to tumour grade, tumour type, involvement of the cardia, procedural difficulties or the need for postprocedural oesophageal dilatation between the two groups. Survival from initial stenting was significantly greater in the restented group (median 24 (range 4–43) weeks) than in the once-stented group (median 9.5 (range 1–84) weeks) ($P < 0.05$). The mean length of stents used in the once-stented group was significantly greater than that of the initial stents used in the restented group (12 versus 10 cm, $P = 0.032$).

Conclusion Inserting a covered stent through a previously inserted uncovered stent is an uncomplicated and well tolerated technique which maintains palliation from obstructing oesophageal carcinoma. The need for restenting cannot be predicted on the basis of tumour characteristics alone.

The 5-year survival rate of patients amenable to 'curative' resection of oesophageal carcinoma is poor, with approximately 20 per cent alive at 5 years¹. The majority of patients with oesophageal carcinoma are elderly, unfit or have advanced disease². Patients are often not suitable for major surgery which carries high morbidity and mortality rates. Less invasive methods of treatment have thus been sought. Tumour destruction can be achieved by laser ablation or photodynamic therapy, although these methods may not be widely available. Pulsion intubation has been the mainstay of palliative treatment, but this carries problems, including tube migration, blockage and oesophageal perforation on insertion, and it still may not allow the patient to swallow satisfactorily.

Insertion of self-expanding metallic stents is a satisfactory method of palliating obstructing carcinoma of the oesophagus. Experience with this method over the past 3 years has confirmed that good palliation may be achieved easily³. However, some patients have developed recurrent obstruction despite an oesophageal stent; restenting these patients appeared to be a useful procedure. The objective of this study was to establish risk factors for patients who require restenting, and to confirm whether restenting is well tolerated and provides adequate palliation.

Patients and methods

Fifty-three self-expanding metallic stents were inserted in a non-selected consecutive series of 42 patients with malignant oesophageal stricture. Forty patients initially received an uncovered 18-mm diameter Strecker stent (Boston Scientific, Massachusetts, USA) and two had covered 18-mm diameter Gianturco–Rosch stents (Cook, Denmark).

All stents were inserted similarly, with the patient in the right lateral position, following lignocaine spray to the pharynx and

sedation. Tumour length was determined by preprocedure contrast study using a lead ruler. Stents at least 2 cm longer than the tumour were positioned under fluoroscopic control over an Amplatz superstiff guidewire (Boston Scientific) after oesophageal dilatation to 12 mm if necessary. Postdeployment balloon dilatation was performed if there was significant stent deformity on postinsertion contrast study. A barium swallow was performed in all patients the following morning.

Thirty-two patients did not require further stenting (once-stented group). Ten patients developed recurrent oesophageal obstruction (restented group). Eight received a covered 18-mm diameter Gianturco–Rosch stent through previous Strecker stents. The remaining two were restented with uncovered 18-mm diameter Strecker stents. One patient was restented a second time using an uncovered 18-mm diameter Strecker stent. The technique employed for restenting was identical to that of the first stenting procedure.

The two groups were compared with regard to survival, patient, tumour and procedural characteristics. Nominal data used in group comparisons were analysed using the χ^2 test with application of Yates' correction. Ordinal data were analysed statistically by means of the Mann–Whitney U test for skewed data and Student's t test for normally distributed data. All P values are quoted according to two-tailed tests of probability.

Results

Indications for stenting

Initial stenting. Forty patients initially received an uncovered Strecker stent and two had covered Gianturco–Rosch stents. Twenty-nine patients had adenocarcinoma of the oesophagus and four had squamous carcinoma, reflecting the practice of treating most squamous carcinomas with radiotherapy. Two patients had bronchial carcinoma invading the oesophagus. Three patients had anastomotic recurrence following gastro-oesophagectomy for adenocarcinoma. Four elderly patients were stented on radiological and clinical grounds alone.

Table 1 Complications of stent insertion

Complication	Stent type and frequency
Food bolus obstruction	S S S
Limited stent expansion	S S S S S S S S S S* G
Stent malposition	S S G G*
Tumour ingrowth	S S S S S S S S S*
Tumour overgrowth	S S G G*

S, Strecker stent; G, Gianturco-Rosch stent. Bold type indicates subsequent restenting. *Indicates a complication in a second stent

Restenting. Ten patients required restenting at a median of 12 (range 2–39) weeks, one being restented twice. Indications for restenting included tumour ingrowth through nine uncovered Strecker stents, tumour overgrowth at the distal end of a covered Gianturco-Rosch stent, and proximal slipping of one Gianturco-Rosch stent revealing the malignant stenosis beyond the distal extent of the stent.

Complications of stenting

Tumour ingrowth occurred through ten Strecker stents, and occlusive tumour overgrowth occurred at the ends of two Gianturco-Rosch and two Strecker stents (Table 1). Food bolus obstruction complicated three cases where a Strecker stent had been inserted, and underlying residual stenosis necessitating balloon dilatation was present in each case. Limited expansion of the stent was observed in 11 Strecker and one Gianturco-Rosch stents, although only one of these required balloon dilatation. Malpositioning occurred with two Gianturco-Rosch stents, both of which slipped proximally following insertion, and two Strecker stents, one where the distal end abutted on the greater curve of the stomach, and one where the distal end was proximal to the oesophageal stricture.

Comparison of once-stented and restented groups

Survival. Eight once-stented patients were alive a median of 14.5 (range 3–100) weeks after stenting, and one patient in the restented group remained alive 90 weeks after initial stenting. Twenty-four once-stented and nine restented patients have died, and only these patients are used in comparisons between the two groups (Table 2). There were no statistically significant differences in the interval from initial stenting to restenting (median 11.5 (range 2–28) weeks), from restenting to death (median 9 (range 1–31) weeks) and from stenting to death in the once-stented group (median 9.5 (range 1–84) weeks). Survival from initial stenting was significantly greater in the restented group (median 24 (range 4–43) weeks) than in the once-stented group (median 9.5 (range 1–84) weeks) ($P < 0.05$).

Patient characteristics. Women were significantly more likely to require restenting than men (once-stented group, 17 men and seven women; restented group, three men and six women, $P < 0.02$). Ages of once-stented (mean 71.8 years) and restented (mean 74.1 years) patients were not significantly different.

Stent and procedural characteristics. The length of the stents used in the once-stented group (mean 12 cm) was

Table 2 Comparison of once-stented and restented groups

	Once stented (n = 24)	Restented (n = 9)†	P
Patients			
Mean age (years)	71.8	74.1	n.s.‡
Sex ratio (M:F)	17.7	3.6	<0.02§
Median (range) survival (weeks)	14.9 (1–84)	26.4 (4–43)	<0.05¶
Tumour*			
Grade (poor/well or moderate)	12:7	4:3	n.s.§
Type (adenocarcinoma/squamous carcinoma)	17:3	7:2	n.s.§
Involvement of cardia (Yes:No)	11:5	4:3	n.s.§
Procedure			
Mean stent length (cm)	12	10	0.032‡
Procedural difficulties (Yes:No)	9:15	3:7	n.s.§
Poststenting dilatation (Yes:No)	2:22	2:8	n.s.§
Repeat barium swallow (Yes:No)	7:17	8:2	<0.02§

*Data not available for all patients; †one patient was restented twice. n.s., Not significant. ‡Student's unpaired *t* test; § χ^2 test; ¶Mann-Whitney *U* test

significantly greater than that used initially in the restented group (mean 10 cm) ($P = 0.032$). There were no significant differences between the two groups with regard to difficulties encountered during first stenting or in the requirement for oesophageal dilatation after stenting. Repeat barium swallows undertaken after the first day following stent insertion, and excluding swallows performed immediately before restenting, were performed significantly more often in the restented than in the once-stented group ($P < 0.02$).

Tumour characteristics. There were no significant differences between the two groups with regard to tumour grade, tumour type or involvement of the cardia.

Discussion

Despite the recent interest in self-expanding stents as applied to oesophageal strictures, this is not a new technique⁴. Many recent studies have shown that stenting malignant oesophageal strictures provides excellent symptomatic relief^{5–15}. In randomized trials, stenting has provided better palliation than both pulsion intubation¹⁶ and laser ablation¹⁷. In many reported series, symptom recurrence in stented patients has been treated by laser ablation^{5,9,16,17}, electrocoagulation and bouginage¹², and the formation of a gastrostomy⁹. Although insertion of a covered stent through an uncovered stent has been proposed as a means of palliating recurrence¹⁵, restenting has been reported only anecdotally^{10–15,18}.

Factors that appear to predispose to restenting include female sex and the use of stents 10 cm in length rather than longer stents. A shorter initial stent may leave uncovered tumour beyond the limit of the stent, or may allow tumour overgrowth at the end of the stent more

readily than a longer stent, thus predisposing to recurrent obstruction. The reasons for the increased need for restenting in women are unclear.

Technical problems with stent insertion do not appear to be related to the subsequent need for restenting, nor does the need for poststenting oesophageal dilatation. An impending need to restent may be indicated by repeated barium investigations. Survival following stenting in the once-stented group was comparable to that of other series using covered^{7,8,14,15,19,20} and uncovered^{5,9,12} stents. Restenting with a covered Gianturco-Rösch stent can almost double the period of palliation achieved by a previously inserted uncovered Strecker stent. Furthermore, restenting is a well tolerated procedure that carries no more risk of complications than initial stenting.

The most common indication for restenting in this series was tumour ingrowth through an uncovered stent. This is a well recognized complication of uncovered stents, the meshes of which are freely transgressed by locally invading tumour^{5,13,17}. Covered stents prevent infiltration, although overgrowth of the end of the stent remains a possibility. Covered stents, however, are more likely to migrate than uncovered stents^{7,10,11,17,20}.

Tumour characteristics such as grade, tumour type and involvement of the cardia do not relate to the need for restenting. Involvement of the cardia may predispose to stent migration¹⁷, and carcinoma at the cardia has even been considered a contraindication to stenting¹. However, stent migration was not a problem in this series, reaffirming that uncovered stents may be preferable to covered stents when the cardia is involved.

The high cost of self-expanding metallic stents may be a deterrent to their routine use in palliation of malignant oesophageal strictures²¹. However, stenting and restenting may be found to be cost-effective methods, considering the need for repeat procedures if pulsion intubation, radiotherapy or laser are methods chosen for palliation¹⁸, particularly as the latter techniques may not be available locally. Insertion of an uncovered self-expanding metallic stent at least 12 cm in length achieves excellent palliation from malignant oesophageal obstruction. Insertion of an uncovered stent 10 cm or less in length predisposes to a need for subsequent restenting, particularly in women. Should restenting be required, palliation of equal duration may be achieved readily by the insertion of a covered self-expanding metallic stent through the existent uncovered stent.

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Management of malignant oesophageal obstruction with self-expanding metallic stents

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Background The use of self-expanding metal stents for palliation of malignant dysphagia is increasing. Experience in 70 patients was reviewed with respect to the value of stenting and management of the complications encountered.

Methods Oesophageal stents were inserted in 70 patients (42 men) of mean age 73 years with malignant oesophageal obstruction. Data regarding stent insertion and degree of dysphagia were gathered prospectively.

Results Seventy-six stents were placed in 70 patients. By the end of the study 57 patients had died and 13 were still alive. Three patients died within 3 days of stent insertion and dysphagia was relieved in 64 of the 67 patients remaining. Stent migration, tumour ingrowth and overgrowth, and food impaction were encountered during follow-up in eight patients.

Conclusion Insertion of self-expanding metal stents for the palliation of malignant oesophageal obstruction is a successful therapy which can be carried out with relative ease. Palliation of dysphagia with an appropriate stent can be expected in up to 95 per cent of patients.

Malignant oesophageal obstruction, due either to intrinsic oesophageal tumours or to extrinsic compression from mediastinal tumours, is not amenable to curative surgery in the majority of patients. The most common and distressing symptom in these patients is dysphagia. Palliation of dysphagia with rigid plastic tubes is unsatisfactory, as they are stiff, often causing trauma at the time of insertion, and have a small lumen with an associated tendency for food impaction. Surgical palliation, chemotherapy and radiotherapy are also associated with significant problems. The use of expanding oesophageal stents has given promising results in the series reported so far^{1–7}, although generally the studies have been carried out in only small numbers of patients. Experience of the use of self-expanding metal stents in the palliation of malignant oesophageal obstruction in 70 patients is reported, with respect to both the value of stenting and the management of complications that were encountered.

Patients and methods

Patients

A total of 70 patients with malignant oesophageal obstruction were treated with oesophageal stents between August 1992 and February 1996. Initial results in 11 of these patients have been reported previously¹. There were 42 men and 28 women with a mean age of 73 (range 51–93) years. The diagnoses are given in Table 1. Three of the patients also had a fistula to the bronchial tree. At the time of reporting, 57 patients had died (mean survival 7 (range 0–54) weeks) and 13 were still alive (mean follow-up 9 (range 4–78) weeks). Data regarding stent insertion and the degree of dysphagia before and within 24 h of stent insertion were gathered prospectively. The degree of dysphagia was graded on a scale of 0–3, where 0 denotes no dysphagia, 1 is the ability to swallow semisolid food only, 2 is the ability to swallow liquids only, and 3 is difficulty in swallowing liquids and saliva. The strictures were evaluated with a contrast swallow before stent insertion. Site, length and diameter of the strictures were assessed. Inoperability was assessed on clinical grounds,

and no patient received palliation with laser therapy before stent insertion.

Technique

A total of 76 stents were inserted in 70 patients; 65 Strecker stents (Meditech–Boston Scientific, Watertown, Massachusetts, USA) and 11 Wallstents (Schneider, Zurich, Switzerland) were used. At the start of the study only Strecker stents were available. All procedures were performed under fluoroscopic guidance using the technique described previously¹. Topical local anaesthesia to the pharynx and intravenous sedation were used. General anaesthesia was not needed in any case. The lesion was predilated with a 20-mm diameter Rigiflex soft-tipped oesophageal balloon (Microvasive–Boston Scientific, Watertown, Massachusetts, USA). Occasionally hydrophilic guidewires were needed to negotiate very narrow strictures. Following balloon dilatation an exchange guidewire was introduced and the stent was introduced over it. Radio-opaque markers on the delivery systems enable accurate positioning of the delivery system across the lesion. There is frequently a residual waist in the stent after deployment. This usually disappears over the subsequent 24 h. Patients were allowed fluids orally 2–3 h after the procedure. Postinsertion chest radiography was not performed routinely. If the stent crossed the oesophagogastric junction, the patient was prescribed a proton pump inhibitor (omeprazole) to prevent symptoms of gastro-oesophageal reflux.

Follow-up

The dysphagia score was recorded 24 h after the procedure and long-term follow-up was obtained at outpatient visits or from the patient's general practitioner.

Table 1 Diagnosis in patients undergoing oesophageal stent insertion

Diagnosis	No. of patients
Squamous carcinoma	21
Adenocarcinoma	8
Carcinoma at oesophagogastric junction	24
Compression from extrinsic malignant nodes	11
Recurrence at surgical anastomoses	6
Total	70

Results

Stent insertion

All strictures were successfully negotiated and dilated. In one patient a 10-cm Strecker stent was found to be too short to cover the length of the tumour, and a further 10-cm stent was inserted successfully at the same sitting. A further patient, who had extrinsic compression from malignant lymph nodes in both the upper and lower thirds of the oesophagus, also required two stents to cover the full extent of the disease.

Failure of deployment occurred in one patient early in the study. Withdrawal of the delivery system, which has a slightly expanded olive-shaped tip, through a stent that was not fully expanded resulted in the stent being accidentally removed as well. This can be avoided by waiting for a few minutes for the stent to widen sufficiently to allow removal of the delivery system.

Outcome

Three patients could not be assessed for degree of dysphagia after stent insertion: one patient died from a pulmonary embolus within 24 h of the procedure and in two patients their general clinical condition deteriorated rapidly and they both died within 3 days of the procedure. Before stent insertion 39 patients had a dysphagia score of 3, and 31 patients had a score of 2. Improvement in dysphagia symptoms occurred in all but three of the remaining patients 24 h after stent insertion, and most were able to eat a normal diet on follow-up. Specifically, 37 patients had a dysphagia score of 0 at 24 h, 27 had a score of 1, and three a score of 2.

The three patients in whom dysphagia did not improve had extrinsic disease causing compression of the oesophagus. Two had been treated with Strecker stents, one of which failed to expand, and the other stent collapsed shortly after the procedure. The third patient, who had required two stents to treat extrinsic disease at two levels, improved within a few hours of the procedure, but the following day still had grade 2 dysphagia. A bolus of food was impacted between the stent and the oesophageal wall; this was removed endoscopically but the patient's general condition deteriorated rapidly and she died 7 days after the procedure.

One patient experienced severe chest pain from gastro-oesophageal reflux, which responded to medical therapy. Minor bleeding occurred from the tumour in two patients. This settled on conservative therapy, and no patient required blood transfusion.

Stent migration was encountered in two cases. In one patient a Strecker stent was placed across a carcinoma at the oesophagogastric junction and the patient then underwent radiotherapy. Tumour shrinkage resulted in the stent falling into the stomach. The stent was subsequently retrieved from the stomach endoscopically. In a second patient a Wallstent that had been placed in the distal third of the oesophagus slipped 3 cm distally, but was still in a satisfactory position.

On long-term follow-up of up to 78 weeks, recurrence of dysphagia due to tumour ingrowth or overgrowth into the stent was encountered in six patients. This occurred after a mean of 22 (range 9–64) weeks. Four patients were treated successfully by the insertion of a further stent, and the remaining two were successfully recanalized with laser therapy. None of these patients encountered recurrent dysphagia before death or the end of the study.

Discussion

Dysphagia is a most distressing symptom and its palliation is an important clinical problem. Palliative surgery is difficult, with a high mortality rate⁸. Balloon dilatation is not very effective⁹, and the same applies to radiotherapy and/or chemotherapy^{10,11}. Insertion of rigid plastic tubes has a perforation rate of up to 8 per cent and a mortality rate of up to 16 per cent^{12,13}.

Metal stents are inserted on a relatively small delivery system with less trauma, and patients may be allowed home the same day. With these stents, effective palliation of dysphagia can be expected in over 90 per cent of patients. Early in the authors' experience, failure to relieve dysphagia in extrinsic nodal disease occurred because of collapse of a Strecker stent; since then, Wallstents, which have a greater radial force to resist extrinsic pressure, have been used. In the third patient who failed to improve after stent insertion, food had become impacted between the stent and the oesophageal wall. Efforts were made to clear this, but the patient died 7 days later from disseminated carcinoma.

Three patients died soon after stent insertion. One died from a proven pulmonary embolus, another from pneumonia associated with an oesophagobronchial fistula, and the third from disseminated metastatic disease. No death was attributable directly to stent insertion.

In cases of oesophagorespiratory fistula, the covered Wallstent represents the optimum treatment¹⁴.

Relatively few periprocedural complications occur²⁻⁷. Severe chest pain was discovered to be a result of the omission of omeprazole. Minor bleeding, presumably due to trauma at the time of stent insertion, will resolve with conservative management. The 10-cm stent may be too short to cover the entire length of a tumour. A second stent can be inserted and longer stents are now available.

It is not yet clear whether covered or uncovered stents are more likely to migrate from their initial position.

Tumour overgrowth or ingrowth into the stents in six patients (9 per cent) with Strecker stents occurred after a mean of 22 (range 9–64) weeks. This is in keeping with the findings of other series²⁻⁷. Acunas *et al.*¹⁵, however, reported tumour overgrowth in 36 per cent of patients, sometimes as early as 2 days after stent insertion. Tumour ingrowth or overgrowth can be treated by insertion of a further stent or by endoscopic laser therapy. Although tumour ingrowth occurred only in patients with Strecker stents, the present results do not necessarily imply that covered Wallstents protect against this.

Insertion of self-expanding metal stents for the palliation of malignant oesophageal obstruction is a successful therapy which can be carried out with relative ease. The Strecker stent is successful in intrinsic oesophageal tumours, but extrinsic nodal disease and oesophagorespiratory fistula are probably best treated with the Wallstent. Palliation of dysphagia with an appropriate stent can be expected in up to 95 per cent of patients.

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Function of the proximal stomach after Nissen fundoplication

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Background After Nissen fundoplication patients frequently report upper abdominal (dyspeptic) symptoms. Theoretically, these symptoms may be the result of changes in function of the proximal stomach as induced by fundoplication.

Methods In this case–control study the response of the proximal stomach to both distension by an air-filled bag and a liquid meal were evaluated with the use of a barostat. In 12 patients after fundoplication and 12 healthy volunteers (age- and sex-matched) perception of symptoms was evaluated during both bag distension and liquid meal stimulus.

Results The minimal distending pressure required to overcome the intra-abdominal pressure was significantly different between patients and controls (mean(s.e.m.) 9.34(0.26) versus 6.73(0.43) mmHg; $P < 0.001$). There was no difference between groups in either the fasted state, volume–pressure curve (compliance) or total symptom score. After ingestion of the liquid meal the adaptive relaxation in the fundoplication group was significantly less than that in controls (mean(s.e.m.) 150(29.2) versus 244(34.8) ml; $P = 0.04$).

Conclusion This study showed that after Nissen fundoplication compliance of the proximal stomach is no different from that in healthy volunteers. Postprandial relaxation of the proximal stomach is decreased and this abnormality may be involved in the pathogenesis of reported dyspeptic symptoms.

In 1956, Nissen¹ described 'eine einfache Operation zur Beeinflussung der Refluxoesophagitis'. Currently, the Nissen fundoplication is the commonest fundoplication employed for gastro-oesophageal reflux disease (GORD) worldwide, providing good results in terms of reflux control^{2,3}, for over 20 years⁴. Despite this success, dyspeptic or upper abdominal symptoms, such as early satiety, postprandial fullness, nausea, vomiting and abdominal distension, appear after Nissen fundoplication in 10–80 per cent of patients^{5–7}. A satisfactory explanation for these symptoms in all patients has not yet emerged but changes in the function of the proximal stomach due to fundoplication may be involved.

The proximal stomach acts as a gastric reservoir and its tone, because of a sustained muscular contraction of the gastric wall⁸, mainly controls the emptying of liquids⁹. Ropert *et al.*¹⁰ found that the barostat is a sensitive and reproducible technique for measuring gastric relaxation. The barostat can also be used to determine the compliance of the proximal stomach. Recently altered compliance and adaptive relaxation was observed in functional dyspeptic patients¹¹ and in type I diabetes mellitus patients suffering gastrointestinal symptoms¹². In the present study, it was hypothesized that both functions of the proximal stomach are altered by the operation and contribute to the postprandial symptoms. Therefore, the aim of this study was to determine the compliance of the gastric wall and the accommodation of the proximal stomach to a liquid meal in patients after Nissen fundoplication.

Patients and methods

Healthy volunteers and patients

Twelve healthy volunteers (six men and six women, mean(s.e.m.) age 37.4(2.84) (range 19–57) years, mean(s.e.m.) body mass index (BMI) 20.1(1.8) kg/m² without any gastrointestinal symptoms) and twelve fundoplication patients (five women and seven men, mean age 40.7(2.85) (range 19–54) years, mean BMI 25.9(0.69) kg/m²) participated in the study after giving written informed consent. The protocol was approved by the medical ethics committee of Utrecht University Hospital. Patients with a 360° Nissen fundoplication who underwent operation between January 1990 and July 1994 were studied. Patients with a previous history of undergoing hepatobiliary-pancreatic surgery (other than cholecystectomy), surgery on the gastrointestinal tract (other than appendectomy, inguinal hernia repair, haemorrhoidectomy) or Nissen fundoplication combined with (proximal) selective vagotomy were excluded. All medication known to influence gastrointestinal motility was discontinued 48 h before the experiment.

Electronic gastric barostat

The barostat measures volume of air within an intragastric bag, maintained at a constant preselected pressure level by an electronic feedback mechanism. When the stomach contracts, the barostat aspirates air from the bag to maintain a constant pressure, and bag volume decreases. When the stomach relaxes, air is injected and bag volume increases.

Injection or aspiration of air was triggered when the pressure in the intragastric bag differed from the preselected pressure by more than 0.2 mmHg. The maximal rate of air flow was 2.4 l/min. The intragastric polyethylene bag (maximal volume 700 ml) was mounted on the tip of a gastric 12-F polyvinyl tube and connected to the barostat. Pressure was measured in the cylinder of the barostat, recorded on a paper polygraph and stored on a computer. The barostat was used to measure compliance of the proximal stomach and response of the proximal stomach to a

liquid meal. Volume was corrected at each pressure level for air compressibility and barostat compliance using an experimentally determined constant (-5.76 ml/mmHg).

Experimental design

The studies were performed after an overnight fast. Participants were asked to relax and the lubricated folded bag was introduced by mouth into the proximal stomach. After the bag was slowly inflated manually with 100 ml of air to unfold it, it was completely deflated and, after a 10-min interval, connected to the barostat. Participants were placed in a 30° recumbent position sitting in a chair with knee supports to assure a comfortable and reproducible position during the experiments (Stokke, Skodej, Norway).

Compliance of the proximal stomach. First, the minimal distending pressure (MDP) was determined. This is the pressure needed to overcome the intra-abdominal pressure and is defined as the first pressure level that provides 30 ml of air in the intragastric bag. Beginning with MDP, pressure was increased stepwise with 2 mmHg increments every 3 min and intragastric volume and perception were measured, elicited by gastric distension at each pressure level. At the pressure level that first provided an intrabag volume of more than 600 ml (maximal volume 700 ml) or when participants reported serious discomfort the pressure was stepwise decreased with 2 mmHg every 3 min and intragastric volume was measured until MDP was reached again.

Accommodation to a liquid meal. After measurement of the compliance of the proximal stomach the intrabag pressure was kept at atmospheric pressure (0 mmHg) for a period of 10 min. Thereafter, MDP plus 1 mmHg was maintained for a period of 45 min before participants ingested the liquid meal. Subjects were asked to drink the 200-ml meal within 1 min. At an intragastric pressure of 1 mmHg above the MDP volume changes and perception were recorded during 90 min.

Meal. The meals, which had a volume of 200 ml, were composed of Nutrilose 34 g (a lactose-free powder milk product; Nutricia, Zoetermeer, The Netherlands), Fantomalt 14 g (dextrine-maltose; Nutricia, Zoetermeer, The Netherlands) with water. The caloric content of the drink was 200 kcal (1.0 kcal/ml) with protein 9.8 g, fat 4.5 g and carbohydrates 30.7 g.

Assessment of gastrointestinal symptoms

Dyspeptic symptoms At the onset of the study, participating patients were asked to complete a questionnaire to score the severity of dyspeptic symptoms that they experienced before and after antireflux surgery. A five-point scale was used: (0) no symptoms present; (1) the symptom is present but not severe (mild); (2) the symptom restricts intake of a normal meal but does not interfere with daily activities (moderate); (3) the symptom does interfere with daily activities (severe); (4) the symptom interferes with daily activities very much and/or patient needs to rest (very severe). The postprandial symptoms addressed were: inability to finish a normal meal, feeling of fullness, nausea, bloating and epigastric pain.

Compliance of the proximal stomach. Perception of gastrointestinal symptoms of nausea, bloating and pain were scored at each pressure level using a visual analogue scale from 0 to 10 (0, absent sensation to 10, very painful sensation). Participants were informed of several possible sensations of nausea, bloating and pain.

Accommodation to liquid meal. Postprandially the sensations of nausea, bloating and pain were scored every 10 min, using a visual analogue scale from 0 to 10 (0, absent sensation to 10, very painful sensation).

Position of intragastric bag

To verify the correct position of the intragastric bag in patients, an upright upper abdominal radiograph was taken after the experiment. Some 2–3 ml of contrast medium was injected in the gastric tube, and the intragastric bag was inflated manually with 300 ml of air. Clipping the catheter prevented the escape of air.

Data analysis

At every 3-min interval the volume was averaged during the last minute and taken as intrabag volume. The mean ascending and descending volume–pressure curves were constructed for both patients and healthy volunteers. The area between the rising and descending volume–pressure curve ('hysteresis') was measured by subtracting the volume of the ascending curve from the volume of the descending curve at 0, 2, 4, 6 and 8 mmHg above the MDP. The preprandial volume (at a pressure of 1 mmHg above MDP) was calculated by averaging the volume over a 10-min period.

The response to a liquid meal was measured by averaging the intragastric bag volumes every 4 min and subtracting the preprandial volume. Total postprandial volume increase (adaptive relaxation) was evaluated by the area between individual postprandial curves and preprandial volume levels from $t=0$ to $t=90$ min (area above the curve (AAC)). This adaptive relaxation reflects the immediate relaxation up to the maximum intrabag volume as well as the long, sustained relaxation towards the preprandial intrabag volume. The slope of the postprandial curve from $t=30$ min to $t=90$ min was determined by linear regression.

The relationship between total score for sensations (nausea, bloating and pain), and pressure levels and intragastric volumes (by grouping the volumes in 100 ml classes) was calculated for both patients and healthy volunteers.

Statistical analysis

The difference in postprandial response and hysteresis of the healthy volunteers and the group undergoing Nissen fundoplication was statistically analysed using the Mann–Whitney U test. MDP and BMI were compared using the Student's t test for independent samples. Analysis of variance was used to compare mean scores for distension sensations, and the slope of the postprandial curve in patients and healthy volunteers. The Wilcoxon signed rank test was used for evaluation of dyspeptic symptoms.

Results

Before operation, all patients had reflux symptoms of heartburn, retrosternal pain and regurgitation. After successful surgical intervention, none of the patients suffered from reflux and only three experienced mild retrosternal pain. Two required intermittent acid suppressing drugs. Mean follow-up was 42 (range 11–58) months. The gastric barostat was well tolerated by the participants and all completed the study. Radiographs showed the bag was positioned in the proximal stomach in all subjects. Furthermore, no signs of paraoesophageal herniation of the fundoplication or a slipped Nissen could be detected on the upper abdominal radiographs.

Compliance of the proximal stomach

BMI was different between patients and controls (mean(s.e.m.) $25.9(0.69)$ versus $20.1(1.8) \text{ kg/m}^2$; $P < 0.01$). MDP was significantly higher in the patients than in normal controls (mean(s.e.m.) $9.34(0.26)$ versus $6.73(0.43) \text{ mmHg}$; $P < 0.001$). As shown in Fig. 1, the pressure–volume curve in response to the stepwise pressure

increase and stepwise deflation showed no difference between the groups. In patients and healthy volunteers, intrabag volumes corresponding with the pressure steps of the inflation curve were different from the deflation curve. In both groups the deflation curve ended at a higher intrabag volume than the volume at the start of the inflation. The area between the ascending and descending

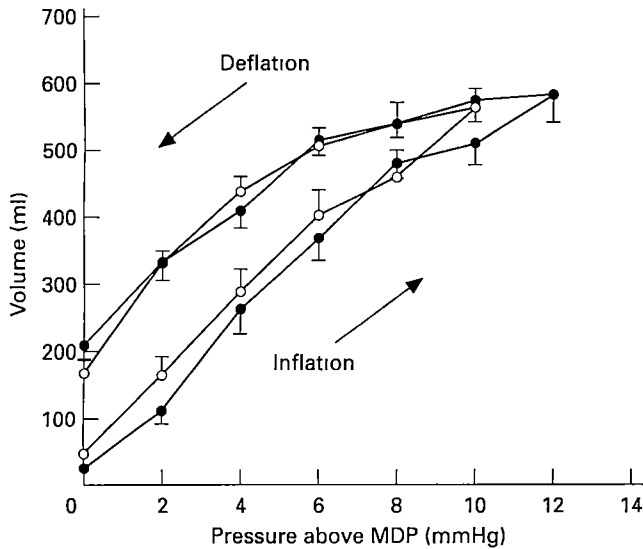


Fig. 1 Mean (s.e.m.) volume-pressure curve of the proximal stomach in healthy volunteers (●) and patients after Nissen fundoplication (○). Neither the ascending part by increasing intragastric bag pressure, nor the descending part of volume pressure showed any difference in steepness of the slopes, indicating compliance of both groups being similar. In patients the pressure was not increased after 10 mmHg above minimal distending pressure (MDP), because this would lead to either an intragastric bag volume greater than 600 ml, or the maximal pressure being reached

pressure-volume curve (hysteresis) was not different between patients and controls (mean 607.5 versus mean 725.2 ml × mmHg; $P=0.3$). The compliance of the proximal stomach was similar in both patients and controls.

Accommodation to a liquid meal

As shown in Fig. 2, the preprandial intrabag volume in patients did not differ from the healthy volunteers (mean (s.e.m.) 184.6(15.1) versus 179.8(17.2) ml). The response to the meal was characterized by an immediate increase in intragastric bag volume, gastric relaxation. The rise of the volume in the intragastric bag was similar in patients and healthy volunteers up to about 30 min postprandially. However, in patients the intrabag

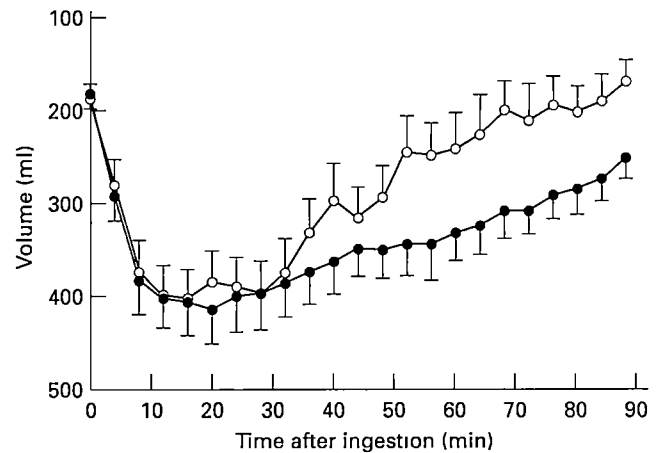


Fig. 2 Mean (s.e.m.) relaxation curve of healthy volunteers (●) and the patients after Nissen fundoplication (○) after ingestion of liquid meal at $t=0$. In Nissen patients the intrabag volume showed a quicker return to preprandial volume

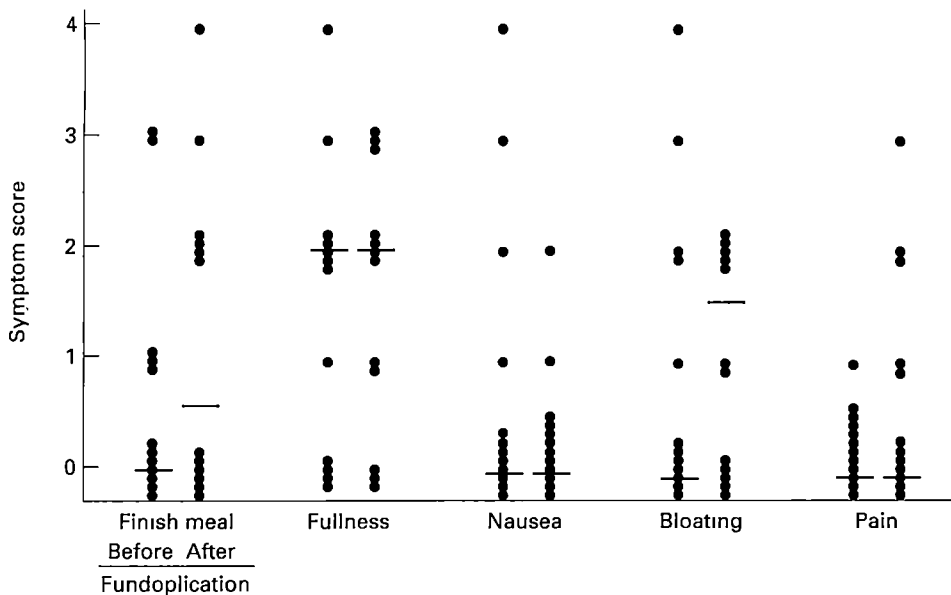


Fig. 3 Score of dyspeptic symptoms in patients after Nissen fundoplication as experienced before and after operation on a five-point scale; score 0, no symptoms to score 4, very severe symptoms. Each plot represents a subject and horizontal bars present median score for each symptom. All but two patients experienced one or more dyspeptic symptoms before and after operation. There was no significant increase in symptom score after fundoplication ($P=0.26, 0.81, 0.20, 0.68, 0.07$ respectively)

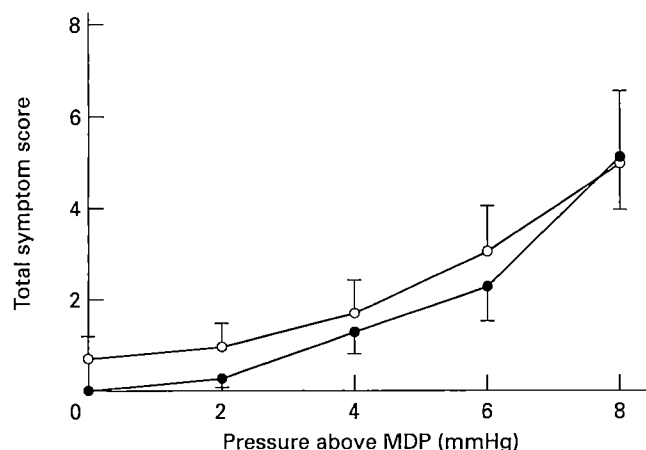


Fig. 4 Mean (s.e.m.) total score of the distension sensations nausea, bloating and epigastric pain in 12 healthy volunteers (●) and 12 Nissen patients (○) with increasing bag pressure. Both groups experienced symptoms with increasing bag pressure, but no difference was found between the groups. Only a minority of participants reached pressure levels more than 8 mmHg above minimal distending pressure (MDP)

volume decreased significantly faster to the preprandial volume than in controls (regression coefficient (s.e.m.) $-3.16(0.25)$ versus $-2.24(0.10)$; $P=0.002$). This resulted in the area between the postprandial time-volume curve and the preprandial volume level being significantly smaller in the patients compared with healthy volunteers (mean (s.e.m.) AAC $150.7(29.2)$ versus $244.4(34.8)$ ml $\times$ h; $P=0.04$).

Symptoms

- (1) All but two patients experienced one or more dyspeptic symptoms before as well as after Nissen fundoplication. No significant difference was found in the symptoms before and after fundoplication (Fig. 3).
- (2) At MDP two patients had mild sensations and none of the healthy volunteers experienced symptoms. During inflation, all patients' as well as healthy volunteers' symptoms increased with increasing intrabag pressure (Fig. 4) and volume. No significant difference in symptom score was observed between the groups ($P=0.3$).
- (3) Postprandially, only four patients, but also four healthy controls, experienced mild symptoms. The symptom scores never exceeded 3 on a scale from 0 to 10. No significant difference could be demonstrated between the groups over 90 min ($P=0.18$). The extent of the postprandial relaxation, AAC, was not correlated with the symptoms.

Discussion

This case-control study examined the function of the proximal stomach after Nissen fundoplication. Only a prospective study can prove that changes in motility of the stomach are because of the fundoplication procedure. The present group after Nissen fundoplication were not studied before operation to use them as their own controls, but age- and sex-matched healthy volunteers were studied.

The Nissen fundoplication has proven to be successful for the control of gastro-oesophageal reflux²⁻⁵. However,

the causes of upper abdominal symptoms as side-effects of otherwise successful antireflux surgery have not been extensively studied. All but two of the present patients experienced dyspeptic symptoms 1-5 years after Nissen fundoplication. Lundell *et al.*¹³ reported that 76 per cent of their patients suffered postprandial satiety and 56 per cent experienced postprandial pain 1 year after antireflux operations and 80 per cent of patients have one or more newly acquired upper abdominal symptoms 1 year after surgery⁵. Other studies with an average follow-up of 5-7 years reported that 10-40 per cent of patients experienced these symptoms^{6,7}. These observations show that post-fundoplication symptoms tend to improve with time¹³. It has been suggested that these symptoms are because of changes in gastric motility^{10,13,15,17,18}, as a consequence of tight fundoplication^{19,20}, surgical damage to the vagal nerve^{16,19,20}, or a combination of the two.

The present studies demonstrated a higher MDP in operated patients. Newton *et al.*²¹ reported a small but significant difference in MDP of 0.5 mmHg between patients with GORD and controls. A much greater difference in MDP between the present groups of 2.6 mmHg was found. This may either be the result of the fundoplication *per se*, a preoperative higher MDP in patients with GORD²¹, or a difference in BMI between the groups as reported recently²². The present patients had a significantly higher BMI than that in the controls. This can also explain the difference in MDP in the study of Newton *et al.*²¹. Furthermore, it is assumed that being overweight predisposes a person to GORD. In future, studies matched for age, sex and BMI are necessary to clarify this point.

The viscoelastic properties of the connective tissue and smooth muscle of the gastric wall are among the factors that determine compliance. Changes in compliance have been observed in patients with non-ulcer dyspepsia¹¹, in patients with type 1 diabetes mellitus¹², and after experimental vagotomy in dogs²³. In this study compliance of the proximal stomach in the Nissen group was no different from that in healthy volunteers. However, subtle vagal nerve damage, a well documented consequence of antireflux surgery^{19,24,25}, cannot be excluded, and if present this apparently has no bearing on compliance. The proximal stomach accomplishes the reservoir function and consists of the fundus and about the proximal-third of the body²⁶. From an anatomical point of view one would expect compliance of the proximal stomach to be lower after fundoplication. This study shows that the fundal wrap is not afunctional and is still able to accommodate to pressure increments. In both patients and controls a bag volume up to 600 ml could be tolerated and no difference in symptom score was observed.

After ingestion of a 200-kcal liquid test meal the intragastric bag volume increased in patients and healthy volunteers in accordance with results obtained by other authors in healthy volunteers¹⁰⁻¹². This suggests that in patients who have undergone surgery immediate relaxation is normal. The slow, sustained adaptive relaxation reflects regain of tone of the proximal stomach by contractile activity^{8,27}. In the patients the intragastric bag volume returned significantly faster towards its preprandial volume. This probably results in accelerated emptying of liquids in the stomach after Nissen fundoplication as described by others^{15,16,18}. These data support the concept that tone of the proximal stomach is a contributory factor responsible for the speeding of gastric emptying of liquids in these patients. Whether

these changes are responsible for the postprandial dyspeptic symptoms in the present group of patients is not clear. Lundell *et al.*¹³ reported that preoperative motility disturbances in terms of gastric emptying can be the cause of postfundoplication symptoms. Indeed, before operation the present patients all reported dyspeptic symptoms but these were not related to gastric motility disturbances before fundoplication.

Whether these data for a liquid meal can be extrapolated to the postprandial symptoms after a solid meal is unclear. The data presently available on perception of adaptive relaxation after ingestion of a meal are all obtained with liquid meals. A 200 ml–200 kcal meal was used because patients, after undergoing fundoplication, report taking smaller meals than usual. It is possible that meals of a different composition and/or volume are more likely to provoke more serious dyspeptic symptoms in patients with an abnormal adaptive relaxation. However, to investigate the response of the proximal stomach to solid meals is difficult when using the barostat technique.

In conclusion, this case–control study showed that the compliance of the proximal stomach in patients who underwent Nissen fundoplication is normal. After fundoplication the adaptive relaxation after ingestion of a liquid meal is decreased, an abnormality that might play a role in the reported dyspeptic symptoms. It is unclear whether the fundal detachment and denervation, the wrap as such, or preoperative GORD contributes to this abnormal postprandial pattern.

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Late results of paraoesophageal hiatus hernia repair with fundoplication

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Background Most published reports on results of surgical treatment for paraoesophageal hiatus hernia have been based on patient questionnaires, and seldom included endoscopy or barium meal examinations.

Methods Eight pure and 14 mixed-type paraoesophageal hernias were evaluated a median of 37 (range 2–241) months after surgical repair. An antireflux procedure was done in 19 cases. Before operation all had endoscopy or barium meal (20 and 19 patients respectively); after operation 19 had endoscopy and 12 also had barium meal examination. Oesophageal 24 h pH monitoring was done in five cases before surgery, and in 11 afterwards.

Results Preoperative symptoms of reflux were reported by 18, and were often accompanied by dysphagia, postprandial vomiting or epigastric pain. Symptoms improved after operation, and 21 of the 22 patients were satisfied with the result. At follow-up examination, a recurrent hernia was found in eight of the 19 patients examined. Four of these hernias were sliding, two were mixed type and two purely paraoesophageal.

Discussion Recurrence of symptoms was associated with persistence of reflux rather than hernia recurrence. Concomitant antireflux procedure is recommended in all operations for mixed-type hiatus hernia, but it should also be considered for purely paraoesophageal hernia if reflux cannot be excluded before operation, or if retro-oesophageal dissection is needed.

The commonest form of hiatus hernia is the sliding type, in which the gastro-oesophageal junction is displaced above the diaphragm. Pure paraoesophageal hernia (gastro-oesophageal junction remaining in the abdomen) is estimated to comprise only 5 per cent of all hiatal hernias¹. The third mixed type has sliding and paraoesophageal components. Sliding hernia is associated with gastro-oesophageal reflux^{2,3}. Whether or not paraoesophageal herniation affects the competence of the gastro-oesophageal junction is debated, as is the need for an antireflux procedure at the time of hiatal repair^{4–7}. Most published reports on results of surgical treatment have been based on patient questionnaires, and only occasionally included observations at endoscopy or barium meal^{4,5,7–9}. Routine endoscopic follow-up was used in only one recent study⁶.

The aim of the present study was to evaluate results from surgical repair of mixed and pure paraoesophageal

hernias with objective methods, including endoscopy, contrast radiography and 24-h oesophageal pH monitoring, and to assess the importance of a concomitant antireflux procedure.

Patients and methods

Twenty-five pure or mixed-type paraoesophageal hiatal hernias were repaired between 1964 and 1994. Mean age of the 12 men and 13 women was 60 (range 35–85) years. In 22 patients this was a primary repair, while three had previously undergone Nissen fundoplication alone for gastro-oesophageal reflux.

Three patients died during follow-up some years after operation (one suicide, two deaths from coronary heart disease). Thus, 22 patients were available for study after a median postoperative follow-up of 37 (range 2–241) months. Before operation 18 had heartburn and/or reflux, with moderate to severe symptoms in 13 (Table 1). Preoperative investigations included oesophagogastroduodenoscopy and/or barium meal in all patients (Table 2), and confirmed eight pure and 14 mixed-type paraoesophageal hernias (Table 3).

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Table 1 Preoperative and postoperative subjective data

	Paraoesophageal hernia (n = 8)		Mixed-type hernia (n = 14)		Total (n = 22)	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Reflux*	6	2	12†	3†	18†	5†
Dysphagia*	5	4	6	3	11†	7†
Vomiting	3	0	7	1	10	1
Epigastric pain	7	5	8	3	15	8
Chest pain	3	1	3	0	6	1

*Mild or greater score in DeMeester and Johnson clinical score^{13,14}; †P < 0.01, preoperative versus postoperative

Postoperative examinations included oesophagogastro-duodenoscopy with biopsy, barium meal examination and 24-h oesophageal pH monitoring (Table 2), and standardized personal interview. Reflux was regarded as pathological if pH was less than 4 for more than 4.2 per cent of the recording interval. Heartburn, reflux and dysphagia were assessed by the patients, and clinical reflux and dysphagia scores were calculated according to DeMeester and Johnson^{10,11}. Symptoms of flatulence and bloating were graded subjectively as 'none', 'mild', 'moderate' or 'severe'¹². Subjective satisfaction with the operative result was assessed as 'satisfied' or 'not satisfied' by the patients.

Nineteen of the 22 patients had undergone hiatus repair, 16 with concomitant antireflux procedure, either Nissen-Rossetti fundoplication¹³ or, in one case, Toupet partial fundoplication¹⁴ (due to absence of peristalsis in the distal oesophagus) (Table 2). The three other patients underwent Nissen-Rossetti fundoplication without hiatal repair. Their hiatal defect was so small that the bulk effect of the fundic wrap was considered to be sufficient to prevent reherniation. Strong non-absorbable sutures were used for hiatal repair and fundoplication, and in the last five patients of the series the hiatal sutures were buttressed with Teflon (C. R. Bard, Massachusetts, USA) pledgets.

Table 2 Preoperative and postoperative examination, and operation performed

	Mixed (n = 14)	Paraeso- phageal (n = 8)	Total (n = 22)
Preoperative examination			
Endoscopy and biopsy	12	8	20
Barium meal	11	8	19
24-h oesophageal pH monitoring	4	1	5
Operation performed*			
Nissen-Rossetti fundoplication	2	1	3
Fundoplication and hiatus repair	11†	5‡	16
Hiatus repair alone	0	1	1
Hiatus repair and anterior phrenopexy	1	1	1
Postoperative examination			
Endoscopy and biopsy	12	7	19
Barium meal	9	3	12
24-h oesophageal pH monitoring	6	5	11

*One hiatus repair in paraoesophageal hernia group was performed via thoracotomy, all other operations via laparotomy.

†Includes one Toupet partial fundoplasty with hiatus repair

‡Includes two repeat Nissen-Rossetti funduplications

The study protocol was approved by the hospital's ethical committee and informed consent was obtained from all patients. Results are presented as median (range). For statistical analysis non-parametric tests were used (Mann-Whitney *U* test and Wilcoxon signed rank test), and contingency table with G^2 statistics.

Results

No patient died within 30 days of surgery. There were five complications: inadvertent splenectomy (one), pneumonia (two) and wound infection (two). Heartburn, reflux, dysphagia, postprandial vomiting and epigastric pain were greatly alleviated after operation (Table 1). Only two patients had more than mild reflux symptoms and any dysphagia was mild and occasional. Satisfaction with the result was expressed by 21 of the 22 patients.

Follow-up endoscopy and barium meal examination showed recurrent hernia in eight of 19 examined patients (Table 3). All three patients without hiatus repair had a recurrent hernia, compared with five of the 16 with hiatus repair. No patient with Teflon pledget buttressing of the hiatus repair had a recurrence, but follow-up was shorter (median 8 (range 2–13) months). Four of 17 examined fundic wraps were disrupted. Recurrent hernia was found in three of four patients with a defective wrap, but only five of 13 with an intact wrap. In four of the latter five patients the hernias were of sliding type, compared with none of the other three. Of the patients who initially had a mixed-type hernia, six of 12 examined had a recurrence, four sliding and one each as mixed or paraoesophageal type. Of the patients who had pure paraoesophageal hernia initially, two had a recurrence, one mixed type and one paraoesophageal.

After operation reflux was demonstrated objectively in two and subjectively in one of eight patients with a recurrent hernia. Respective figures for 11 patients without a recurrent hernia were two and three. In patients who had an antireflux procedure, reflux was observed after operation in three of 17, compared with one of two without. Reflux symptoms were reported by two-thirds of those with a defective wrap, or defective wrap and recurrent hernia, compared with none of those with only a recurrent hernia.

Of three patients without a concomitant antireflux procedure, one initially had a mixed-type hernia and no preoperative oesophagitis. The patient's main symptom was vomiting with haematemesis (due to irritated mucosa in the herniated stomach). After operation the hernia did

Table 3 Preoperative and postoperative objective data

	Paraoesophageal hernia (n = 8)		Mixed-type hernia (n = 14)		Total (n = 22)	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Oesophagitis*	0	0	7	3	7	3
Objectively observed reflux*†	1	1	8	3	9	4
Type of hiatal hernia						
None	0	5	0	6	0	11
Sliding	0	0	0	4	0	4
Mixed	0	1	14	1	14	2
Paraoesophageal hernia	8	1	0	1	8	2

*Before operation eight patients with paraoesophageal hernia and 12 with mixed-type hernia were tested and/or underwent endoscopy; after operation the numbers were seven and 12 respectively. †Oesophagitis and/or abnormal 24-h pH monitoring

not recur, but he had moderate symptoms of reflux and oesophagitis, which responded to H₂ blockers. Both of the other patients had a paraoesophageal hernia and were symptom-free at follow-up.

When an antireflux procedure was used, the symptoms of reflux disappeared in ten of 12 patients who initially had a mixed-type hernia and in three of five with a paraoesophageal hernia. Reflux symptoms were diminished in all but two cases (Wilcoxon signed rank test, $P = 0.004$).

Symptomatic flatus and/or bloating was reported by 12 of 22 patients before operation, but only nine afterwards. All symptomatic patients both before and after surgery were in the group who had a concomitant antireflux procedure. Postoperative symptoms were moderate in three but severe in none.

Discussion

In the present study the complication rate was similar to previous reports^{6-8,15}. Preoperative symptoms were greatly relieved and all but one of the 22 patients were satisfied with the outcome. Nevertheless, eight of the patients had recurrence of the hernia. One-half of the recurrent hernias were sliding, possibly because of the fundoplication. Mixed-type hernias showed a greater tendency to recur. In one earlier study⁸ the recurrence rate was only 11 per cent, but objective evaluation was confined to symptomatic patients. Other authors¹⁶ reported a 29 per cent recurrence rate after operations for postfundoplication paraoesophageal hernia. In the earliest report of routine endoscopic follow-up⁶, the recurrence rate was only 3 per cent after a mean of 2.5 years. The present results show that fundoplication alone, without hiatus repair, is inappropriate for a paraoesophageal hernia. Even if such cases are excluded from the series, the recurrence rate was still five of 16. Crural repair using Teflon-buttressed pledgets seems promising. So far, no recurrent hernias have been reported, but follow-up is short. One difference from previous reports⁶ was that retro-oesophageal dissection was avoided and anterior hiatus repair used.

Symptoms and endoscopic signs of reflux and type of hernia may not be reliable methods of evaluating the need for a concomitant antireflux procedure. Some authors^{6,8} recommend antireflux surgery only if reflux can be demonstrated objectively, but in their series severe reflux symptoms developed in 2 per cent of cases although there was no preoperative oesophagitis. Others⁵ found pathological preoperative pH scores so often in patients with a pure paraoesophageal hernia, even in the absence of oesophagitis, that antireflux measures should be routine. Reflux in these conditions, however, may be secondary and cured by hernia repair. Other arguments in favour of concomitant antireflux surgery include the difficulty of confirming reflux before or during operation, and the possibility that surgery may weaken the physiological antireflux mechanism⁷. In some cases it may also be difficult to assess the exact location of the gastro-oesophageal junction. Fundic wrap provides extra bulk at the level of gastro-oesophageal junction and thus anchors it in the subdiaphragmatic position¹⁷.

The present experience, in accordance with others^{5,7,17}, suggests that an antireflux procedure should be added to all operations for mixed-type hernia and should also be

considered in cases of pure paraoesophageal hernia, if reflux cannot objectively be ruled out before surgery, or if retro-oesophageal dissection (that weakens posterior attachments of the gastro-oesophageal junction area) is needed during the operation. In this study, return or persistence of preoperative symptoms was not usually associated with recurrence of the hernia, but rather with persistence of reflux. An intact fundoplication seemed to give some protection against recurrent herniation; if the hernia recurred it was often asymptomatic and of sliding type. Concomitant fundoplication may stabilize the gastric wall and prevent massive or more awkward herniation. Fundoplication-related symptoms were mild and occasional, as was also found in long-term follow-up after Nissen fundoplication for reflux oesophagitis¹². To avoid the dangers of repeat surgery in the hiatal region^{18,19} it would also seem advisable to make the repair complete at the primary operation. Correction of a paraoesophageal hernia should be preceded by contrast and endoscopic examinations and 24-h recording of oesophageal pH and oesophageal manometry, to tailor surgery to individual requirements.

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Novel approach to the treatment of intestinal fistula in the inaccessible abdomen: transbursal end-to-side duodenogastrostomy

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Background Treatment of enterocutaneous fistula in patients with intra-abdominal sepsis and a surgically inaccessible abdomen is frequently unsuccessful.

Methods A new approach has been devised: total disconnection of the proximal digestive tract, which can be performed through the bursa omentalis without entering the scarred abdomen.

Results The procedure was carried out in four patients with high-output small bowel fistula and an inaccessible abdomen. Output of fistulas stopped promptly, recovery from intra-abdominal sepsis was achieved, the abdomens became accessible again and continuity of the digestive tract could be restored in all patients after intervals of 2–5.5 months.

Conclusion Transbursal end-to-side duodenogastrostomy is a useful procedure when traditional surgical interventions have failed or cannot be applied.

Most enterocutaneous fistulas occur as a result of dehiscence of suture lines or from surgical trauma during re-exploration for severe intra-abdominal infection¹. Traditional surgical treatment of persisting enterocutaneous fistula consists of diversion of intestinal effluents away from the defect by exteriorization of the digestive tract proximally to the defect, or by exteriorization of the defect itself^{1–8}. However, exteriorization of the digestive tract is nearly always impossible when the abdomen has become inaccessible. Re-exploration under these circumstances frequently leads to the occurrence of even more leaks^{6,7}. It is for these uncommon but, when left untreated, usually fatal situations that a rather radical but surprisingly effective solution has been devised: total disconnection of the proximal digestive tract through the bursa omentalis, which is nearly always surgically untouched and is generally not disturbed by the intra-abdominal infection.

Patients and methods

Patients

Between May 1995 and May 1996 total disconnection of the proximal digestive tract was performed in four patients (one woman and three men) aged 39–57 years with persisting intestinal fistula and intra-abdominal sepsis. In one patient the problems had started after small bowel perforation during treatment of a ruptured abdominal aortic aneurysm. In the remaining three patients the initial cause was a suture line dehiscence, in two after anterior rectal resection for cancer and in one after colectomy for toxic ulcerative colitis. All patients were transferred from outside hospitals where experienced surgeons had performed several relaparotomies, ranging from one to six, in an attempt to solve the problem. During these relaparotomies one or more iatrogenic small bowel perforations occurred and eventually all abdomens were declared inaccessible. At admission, all patients had uncontrolled, high-output, small bowel fistula posing a permanent serious threat to the surrounding abdominal skin and causing uncontrolled insensible losses. In three patients an intestinal fistula was present in large abdominal wall defects, in two patients after open management

of the abdomen for persisting peritonitis and intra-abdominal sepsis.

During the period between the total disconnection, as described below, and the restoration of the digestive tract, intravenous feeding was permanently installed. Because of the ulcerogenic potential of the continuous flooding of the stomach with alkaline contents resulting from the operation, all patients received maintenance acid-suppressing therapy with omeprazole. Intravenous catheter sepsis was managed by early removal of the catheter and introduction of a new catheter a few days later.

Operation

The basic principle behind the technique of total disconnection of the proximal digestive tract is the observation that in a completely scarred and adhesive abdomen, and even in the presence of enterocutaneous fistula and intra-abdominal abscess, the bursa omentalis remains virgin territory with an undisturbed anatomy and proper surgical dissection planes.

Through a small, 6–8-cm long, median incision just below the xiphoid, the upper part of the abdomen is opened. Immediately below this incision the left lobe of the liver and the stomach are identified. The lesser sac (bursa omentalis) is then opened by dividing 5–10 cm of the gastrocolic ligament along the greater curvature of the stomach (Fig. 1). Near the caudal edge of the pancreas the transverse mesocolon is incised just left of the aorta and the ascending duodenum and duodenojejunal flexure are identified and carefully mobilized. By transecting the ascending duodenum and closing the distal end by means of a GIA (US Surgical, Norwalk, Connecticut, USA) stapler, total disconnection of the proximal digestive tract is achieved. An end-to-side duodenogastrostomy is subsequently performed and a tube gastrostomy is added for decompression (Fig. 2).

Results

After total disconnection of the proximal digestive tract, output of all fistulas stopped promptly and almost completely (except for the production of mucus), and skin irritation healed. All patients recovered quickly from intra-abdominal sepsis and were transferred temporarily to the outside hospital for further convalescence. No operation-specific complications were encountered. Minor electrolyte disturbances were occasionally seen and could be easily corrected by supplements to the intravenous

feeding. Although in two patients mild changes of liver function were noted, these were not dissimilar to those commonly seen in other patients on long-term intravenous feeding. Intravenous catheters had to be changed regularly because of catheter-related sepsis or blockage, but in only one patient did this lead to an earlier than planned date for the restorative operation.



Fig. 1 Opening of the bursa omentalis by dividing 5–10 cm of the gastrocolic ligament along the greater curvature of the stomach

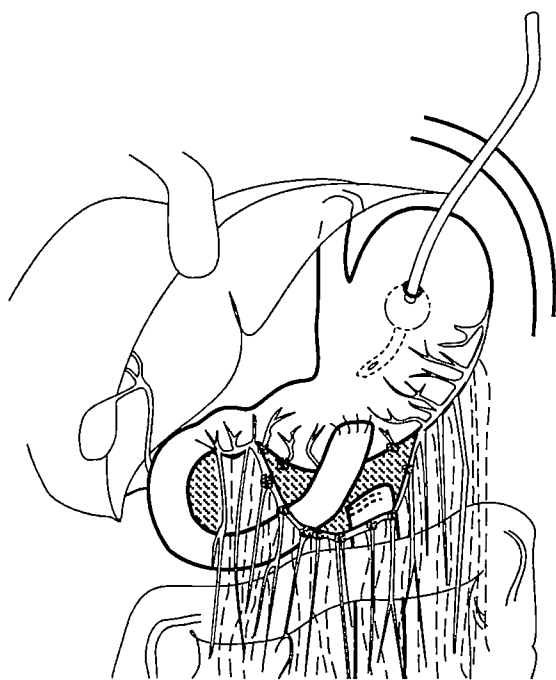


Fig. 2 Total disconnection of the proximal digestive tract by means of an end-to-side duodenogastrostomy and a tube gastrostomy for decompression

After intervals varying from 2 to 5.5 months, all four patients underwent further surgery; the abdomens were explored without undue problems and continuity of the digestive tract was restored. In two patients large abdominal wall defects were simultaneously reconstructed using relief incisions bilaterally as described by Ramirez *et al.*⁹.

Ultimately, all patients were discharged in good health. Some 4–12 months after restoration of the digestive tract all four patients were well.

Discussion

The traditional treatment of intestinal fistula, comprising control of fistula discharge, elimination of intra-abdominal infection, parenteral nutrition and definitive surgery later on if necessary, is usually successful. Definitive surgery, if necessary, should not be undertaken in the first weeks after the onset of the fistula because of the high risk of iatrogenic damage, recurrent fistula, recurrent intra-abdominal infection and mortality.

However, in patients with uncontrolled peritonitis and severe intra-abdominal sepsis, early surgical treatment is sometimes inevitable. Abscesses should be drained and, if required, proximal stomas have to be constructed, or exteriorization of the ends of the compromised bowel or defect has to be performed. Nevertheless, mortality rates often exceed 50 per cent^{1–8}. Mulholland and Delaney⁷ have advocated a totally diverting proximal jejunostomy in the surgical therapy of persisting intestinal fistula. This procedure seems to be a useful measure where long segments or multiple areas of small bowel are affected.

A major disadvantage of the techniques described above, especially in an abdomen scarred and adherent as a result of persisting intra-abdominal infection, is the frequent injury to, and consequent sacrifice of, more segments of uninjured bowel. In a totally inaccessible abdomen these techniques are not applicable and the outcome is nearly always fatal.

Therefore, a new surgical technique was developed to construct a totally diverting, ultimately proximal stoma in an abdomen ruined by persisting intestinal fistula and intra-abdominal infection.

Fortunately, the bursa omentalis is not often disturbed by the intra-abdominal infection and is surgically untouched. The abdomen can be explored through a relatively small median incision above or in the upper part of the disrupted former laparotomy wound or abdominal wall defect. By performing a duodenogastrostomy and a tube gastrostomy, all intestinal effluents can be collected easily. Nursing care of a patient with a tube gastrostomy, especially when a large abdominal wall defect is also present, becomes much easier than when an end jejunostomy is constructed. The procedure described was successful in all four patients. They recovered quickly from abdominal sepsis and continuity of the digestive tract could be restored at a later stage.

Although it could be theorized that total upper gastrointestinal diversion would lead to such adverse effects as duodenal ulceration, acute pancreatitis and severe liver dysfunction, none of these events occurred. The number of patients for whom this procedure has been developed, i.e. those with high-output enterocutaneous fistula and a surgically inaccessible abdomen, is small. Therefore it will take further time and experience to establish the real value of this novel approach. The limited experience thus far, however, has been promising, leading to the

conclusion that, in the case of persisting intestinal fistula in an inaccessible abdomen, total disconnection of the proximal digestive tract can solve a major surgical problem where more traditional surgical procedures have failed or cannot be applied.

Acknowledgements

The authors thank I. G. J. Janssen for drawing *Figs 1* and *2*.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Oral erythromycin improves gastrointestinal motility and transit after subtotal but not total gastrectomy for cancer

Sir

We agree with Altomare *et al.* (*Br J Surg* 1997; 84: 1017–21) that the Roux stasis syndrome is partly a result of efferent limb dysmotility. The authors propose that one mechanism for this may be the duodenal limb interfering with motility of the jejunal limb. Fig 4 in their article implies that contractions are propagated across the end-to-side anastomosis and, subsequently, in a retrograde direction along the efferent limb. We have investigated this phenomenon using a canine model. Four dogs underwent distal gastrectomy with Roux-en-Y reconstruction and 12 months later underwent a second laparotomy with placement of bipolar serosal electrodes across the jejunojejunostomy. Myoelectrical recordings were obtained in the fasted and fed states on a weekly basis for up to 5 months. Data were recorded on tape and replayed to a polygraph to identify migrating motor complexes (MMCs), slow waves and spike potentials. Throughout the study, up to 17 months after surgery, there was not a single episode of conduction of myoelectrical activity across the jejunojejunal anastomosis. All MMCs, slow waves and spike potentials in the duodenal limb propagated distally but were blocked at the anastomosis. There was no evidence of retrograde MMC propagation up the jejunal limb. Histological examination of each anastomosis demonstrated mucosal continuity but no evidence of muscle or neuronal continuity.

It is likely that retrograde contractions in the efferent jejunal limb are a result of ectopic pacemakers rather than conduction from the afferent duodenal limb.

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Author's reply

Sir

We were interested to read of the experiment carried out by Messrs Woodward and Sillin and agreed that it is possible that retrograde contraction in the efferent Roux limb may be a result of ectopic pacemakers rather than retrograde contraction propagated across the end-to-side anastomosis. The phenomenon is difficult to demonstrate in humans and is it no surprise that no retrograde MMCs were observed in the Roux limb in their canine model because the gastric pacemaker area would be spared and remain active. It could therefore impose its higher frequency of depolarization on the remaining intestinal tract. Only at the level of the ileo-ileal anastomosis did they find motility impairment, probably because of interference with electrical activity coming from the duodenum. We described antiperistaltic MMCs in the Roux limb only after total gastrectomy and, in this case, the remaining higher frequency pacemaker is located in the duodenum. It is to be expected that

different gastrointestinal operations may result in different motility findings.

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Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis

Sir

We read with interest the paper by McKay *et al.* (*Br J Surg* 1997, 84: 1239–43) regarding the use of lexipafant as an adjunct to full supportive care in the early management of patients with severe acute pancreatitis. The primary endpoint of the study was the degree of organ failure, which is more realistic than mortality in the patient population chosen.

The authors state that lexipafant may be a 'useful adjunct to full supportive care' but give few details as to what supportive care. This is particularly important in a multicentre study involving 50 patients from 11 hospitals, when aspects of supportive care could have been significantly different between centres. The components of the Marshall organ failure scoring system may themselves be altered by supportive therapy and this needs to be standardized to make such a comparison valid. There is no mention of the requirement for intensive care, use of vasopressor therapy, incidence and duration of mechanical ventilation, sedation policy used and its impact on the Glasgow Coma Score, criteria for and the frequency of renal support, and the policy for haematological support. There is no reference to the incidence and type of surgery that some of the patients presumably required, especially those with infected pancreatic necrosis. There is no mention of the type and duration of nutritional support, whether selective gut decontamination was used, or whether somatostatin analogues were employed. It would be interesting to know details of the relative antibiotic usage between the groups. (Presumably the study was designed before the publication of two randomized studies suggesting benefit of antibiotics in severe acute necrotizing pancreatitis^{1,2}).

Without these details it is difficult to put the study into the correct context. Although none of the above interventions has been shown incontrovertibly to affect mortality^{3–6}, they may easily have affected significantly the outcome measure chosen.

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Authors' reply

Sir

Drs Wyncoll and Beale rightly state that there was no standardization of supportive care between the various centres involved. Our policy in this and previous studies was to leave the day-to-day management of these patients to local medical staff. In acute pancreatitis, where little evidence-based consensus exists regarding many aspects of treatment, it would be impossible to conduct a multicentre study in any other way. With regard to the incidence and type of surgery employed, no patient received surgical intervention within 7 days of study entry. This was the time period over which the primary endpoints were assessed and, therefore, these details would not have influenced the results. Selective gut decontamination, octreotide therapy and enteral feeding were not employed during the first week of illness in any patient.

No hospital was employing a policy of prophylactic antibiotic therapy at that time and in neither of the two randomized trials^{1,2} was there a significant effect of antibiotic therapy on organ failure. There is probably no hard evidence that the use of antibiotics would have influenced the results of our study. As the authors rightly state none of the above interventions has been shown conclusively to affect mortality, but it is also worth noting that no therapeutic intervention has been shown to have a significant influence on organ failure either. This is the justification for the current interest in lexipafant which is the first agent to influence organ failure in patients with this condition.

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Outcome of palliative and gastric bypass surgery for pancreatic head carcinoma in 126 patients

Sir

We read with interest the paper by van Wagenveld *et al.* (*Br J Surg* 1997; 84: 1402–6) reporting the outcome of palliative combined biliary and gastric bypass surgery in 126 patients with pancreatic head carcinoma. The overall mortality and morbidity rates of 2 and 27 per cent respectively are to be commended.

The role of routine preoperative endoscopic internal biliary drainage before definitive surgical intervention remains controversial. In a large retrospective study of patients undergoing surgery for pancreatic carcinoma, Trede and Schwall¹ showed that patients who underwent preoperative endoscopic internal stenting had a reduced incidence of postoperative infective complications. Lygidakis *et al.*², in their prospective randomized trial, reported significantly reduced intraoperative bleeding, incidence of bacteraemia and biliary infection with endoscopic internal biliary drainage. Lai *et al.*³, however, reported no improvement in postoperative morbidity or mortality in patients who had preoperative endoscopic drainage for malignant obstructive jaundice compared with those who had no preoperative decompression. In this series preoperative endoscopic biliary drainage was performed in 72 per cent of patients, with no significant difference in postoperative morbidity or mortality rates compared with the 28 per cent of patients in whom preoperative biliary drainage was not achieved.

Another controversial issue with regard to biliary bypass surgery is whether to perform a simultaneous prophylactic gastroenterostomy. Although 30–50 per cent of patients with pancreatic carcinoma have nausea or vomiting at the time of presentation^{4,5}, definite mechanical obstruction of the duodenum has been reported to be present in only 5 per cent of patients^{4,6}. Delayed gastric emptying and discharge from hospital have been reported following gastroenterostomy and, therefore, some authors do not favour its routine use^{7–9}. In our own practice, gastroenterostomy is performed only if there is evidence of definite or impending duodenal obstruction on preoperative barium studies, or if there is compression of, or encroachment into, the duodenum by tumour seen at the time of surgery. Employing this policy, 23 per cent of patients required a gastroenterostomy at the time of biliary bypass and, of those who did not, only 6 per cent presented subsequently with duodenal obstruction necessitating bypass¹⁰.

It is clear from recent studies that surgical biliary bypass procedures can be performed with acceptable morbidity and mortality rates in patients with obstructive jaundice secondary to irresectable pancreatic carcinoma. There remains, however, considerable debate as to the relative merits of bypass surgery and non-operative treatment of these patients¹¹. We await with interest the results from the authors' present randomized trial comparing surgical with endoscopic palliation in these patients.

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Genetic instability in patients with metachronous colorectal cancers

Sir

I read with interest the paper by SenGupta *et al.* (*Br J Surg* 1997; 84: 996–1000) demonstrating microsatellite instability in metachronous colorectal cancers. There are two points of concern. First, although not rigorously defined, it is generally

accepted that, to demonstrate microsatellite instability, shifts at two or more microsatellites are required^{1,2} and, therefore, the authors should have confined their discussion to eight cancers and not 17. Second, although microsatellite instability can be demonstrated in up to 28 per cent of sporadic colorectal cancers, it occurs more frequently in proximal cancers (up to 35 per cent), and 87 per cent of all cancers demonstrating microsatellite instability are proximal to the splenic flexure³. In the study, population proximal cancers accounted for 11 of 24 cases, whereas the control group contained three of 15. Given these proportions one would therefore expect seven cancers from the study population to exhibit microsatellite instability and four in the control population. In view of the small numbers in this study, do the results simply illustrate sample bias reflecting the already known distribution of microsatellite instability in colon cancers?

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Authors' reply

Sir

We thank Mr Potter for his interest in our paper. There were in fact 12 cancers (not eight) that showed microsatellite instability at two or more loci, and the control group contained a total of 14 cancers not 15. To date, there is no consensus as to the number or choice of markers required for screening to assess microsatellite instability. Consequently, some groups¹ have used four markers and others² up to 34. Furthermore, there is evidence to suggest that some markers are more prone to instability than others³. Unless a common set of microsatellite repeat loci can be identified that ensures the detection of all microsatellite instability, a lack of instability may indicate only that not enough appropriate markers have been investigated. Conversely, finding instability even at one locus may be indicative of a fault in some part of the DNA repair mechanism. Indeed, studies using cell lines with mutations in different genes associated with DNA repair express varying degrees of microsatellite instability⁴. Some lines show high mutation rates at both microsatellites and DNA coding sequences, whereas others show only a low level of instability but a high rate of mutation at coding sequences. Hence, despite a low level of instability, the underlying repair gene mutation is pathologically important. In patients with multiple primary cancers, 89 per cent show microsatellite instability, and this is often only apparent at a single locus⁵. In our study all 17 cancers that showed microsatellite instability were included and our finding of a low level in metachronous colorectal cancer is in agreement with others⁶.

Mr Potter's second point of concern arises from data by Thibodeau *et al.*¹ which indicates that 28 per cent of sporadic colorectal cancers at all sites show microsatellite instability. Based on this percentage they made a theoretical calculation that the expected number of cancers showing microsatellite instability in our study would be seven (i.e. 28 per cent of 24 cancers in total). However, Thibodeau *et al.*¹ derived the figure of 28 per cent by including ten cancers which show instability at only one locus. If only cancers with instability at multiple loci are

considered, just 17 per cent (15 of 90) of sporadic colorectal cancers would be classified as having microsatellite instability, and the expected number of cancers showing instability at two or more loci in our study group would be 17 per cent of 24, i.e. four cancers, not seven as calculated. The difference in the number of cancers with microsatellite instability at two or more loci in our study (12 of 24) and sporadic cancers with instability at two or more loci in the study by Thibodeau *et al.*¹ (15 of 90) is highly significant ($\chi^2=11.67$, 1 d.f., $P<0.001$). If cancers with microsatellite instability at one locus are included, the difference in cancers with instability in our study (17 of 24) and sporadic cancers with instability in the study by Thibodeau *et al.*¹ (25 of 90) is also highly significant ($\chi^2=15.13$, 1 d.f., $P<0.0005$). It is inappropriate to compare our data with that of Thibodeau *et al.*¹ with regard to the distribution of the cancers as the location of the metachronous cancer would be affected by surgical intervention of the initial cancer. Thibodeau *et al.*¹ also included synchronous cancers, which have a higher incidence of microsatellite instability than sporadic cancers⁵. Our investigation included ten initial cancers and 14 metachronous cancers and, of the ten initial cancers, seven were in the proximal colon, of which six showed microsatellite instability in two or more loci. Therefore, our results do not merely reflect the known distribution of microsatellite instability in the colon. Mr Potter's letter highlights the difficulty in comparing data between different studies where, although a number of parameters and findings may be similar, they are not necessarily interchangeable.

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Amylase concentration of drainage fluid after total gastrectomy

Sir

I was interested to read the study by Sano *et al.* (*Br J Surg* 1997; 84: 1310-12) where they suggest that amylase determination from drainage fluid on the first day after operation may predict accurately the development of a pancreatic fistula and help plan appropriate management. I have some reservations regarding this interpretation of the study and, in particular, regarding its usefulness in clinical practice.

At the suggested cut-off level of 4000 units 19 of 27 patients 'at risk' did not develop a pancreatic fistula, whereas five of 67 patients deemed 'not at risk' did. Accordingly, sensitivity,

specificity and positive predictive values of 62, 77 and 30 per cent respectively were calculated. It may be observed that these results are just a little more accurate than tossing a coin.

The consequences drawn for clinical management are non-committal. When amylase is high, drains are left for at least 7 days. When amylase is low, drains are also left in place for several days. Only in the event of a fistula becoming clinically apparent are drains replaced under radiological guidance. In summary, the authors leave drains placed during surgery for several days and take action only when a fistula becomes clinically obvious. In almost all instances pancreatic secretions will gradually resolve before drains are slowly removed. I would therefore agree with the authors that it is best to leave drains in place for 5 days, i.e. the time it usually takes the presence or absence of a pancreatic fistula or anastomotic leak to be seen clinically. The additional effort and cost of amylase determinations from drainage fluid does not seem warranted. In the present report it does not allow more efficient clinical management.

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Authors' reply

Sir

We are grateful for Dr Lehnert's interest in our study. As he correctly pointed out amylase determination is not an 'accurate' method for the prediction of pancreatic fistula. It does, however, give useful information for drain management in the early post-operative course.

A high-amylase content in the drainage fluid alerts to the possibility of the development of a pancreatic fistula, and we usually apply continuous suction to the drain instead of waiting for a clinically obvious fistula to develop. We believe this mini-

mizes the size and change of infection of the incipient fistula. Repeated determinations on subsequent days may provide additional information for drain management. Since 1995 the routine use of amylase determination in drainage fluid has allowed the successful treatment of patients with pancreatic fistula.

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Subfascial endoscopic perforator surgery is associated with significantly less morbidity and shorter hospital stay than open operation (Linton's procedure)

Sir

I enjoyed the article by Stuart *et al.* (*Br J Surg* 1997, 84, 1364–5) on the use of the subfascial endoscopic surgery for incompetent perforating veins in the lower leg. May I, as an alternative, suggest a direct approach to perforating veins after identifying the exact site with duplex ultrasonography. This approach can be made through an incision similar in size to that required for SEPS and, in my experience, such small incisions almost invariably heal without problems, even when made through damaged skin. Such surgery can be done on a day-case basis.

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Book reviews

Year Book of Plastic, Reconstructive and Aesthetic Surgery – 1997

S. H. Miller (ed.). 234 × 157 mm. Pp. 350. Illustrated. 1997 St Louis, Missouri: Mosby. £59.95.

The *Year Book* series began in 1901 when it was felt that the literature of medicine and related disciplines had become so voluminous that no single individual could read and place in perspective every advance in a major specialty; this is even more true today. There are 47 relevant journals reviewed for this *Year Book*. The editor and his associate editors all work in the USA which probably accounts for the bulk of the material (144 of 204 abstracts) being from the North American literature. The text is laid out in a standard fashion with chapters headed 'Congenital Neoplastic Inflammatory and Degenerative Conditions', 'Trauma', 'Aesthetic Surgery', 'The Breast', 'Flaps and Tissue Expansion', and 'General'. Each abstract has at its end a comment from one of the editors. This is a nice touch and many of the remarks are very enlightening. This book will allow the specialist plastic surgeon to dip into the literature of areas outside his own particular interest and in that it succeeds in its aim. Trainees may also find that the editorial comments put the abstracts into context.

J. D. Watson

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Tools of the Trade and Rules of the Road – A Surgical Guide

E. A. Deutch (ed.). 234 × 154 mm. Pp. 367. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. £27.

This is a handy little book addressing all the practical issues relating to the operating theatre and the planning and execution of a surgical procedure. It addresses such issues as 'how long should I scrub?', 'when should I use a drain?', and 'how should I explore the abdomen in cases of trauma?'. It contains a lot of good sound surgical common sense and is liberally and well illustrated with very clear line drawings. It is intensely practical and would be of considerable value to basic surgical trainees as they start out on their surgical careers. However, one wonders about the book's true identity. Is it seeking to be an operative textbook, as it covers methods of anastomosing bowel? Is it seeking to be a guide to theatre behaviour, as it covers intubation and lines of responsibility within the theatre complex? Or is it seeking to be a practical handbook, as it covers arterial cannulation? I am also not entirely sure about the level of experience at which the authors aim, as they address both knotting techniques and dealing with penetrating cardiac ventricular injuries, items that are surely at either end of the surgical scale. However, it is a most entertaining book, especially if one is fascinated with American terminology, for within this modest little text one is introduced to the Rocky Davis incision, Roundmanship, and the joys of Lagniappe. Readers will have to explore the volume for themselves if they wish to be thus educated.

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Hernia Repair: Open vs Laparoscopic Approaches

G. J. Maddern, J. R. Hiatt and E. H. Phillips (eds). 253 × 195 mm. Pp. 243. Illustrated. 1997. Edinburgh: Churchill Livingstone. £60.

Inguinal hernia repair by the laparoscopic route remains a minority interest throughout the UK, although there are recognized centres of expertise. This multi-authored book of 20 chapters covers inguinal hernia repair in all its guises. Separate chapters are devoted to each of the well recognized open techniques, such as a darn repair, the Shouldice procedure and the Lichtenstein mesh repair. Both transabdominal and extraperitoneal 'laparoscopic' repairs are covered in some detail with superb line drawings and innumerable top-quality colour photographs. The description of each method is very readable and I particularly enjoyed many of the authors' subtle tips to improve technique. While this volume offers a comprehensive and up-to-date guide to hernia repair, it is only in the final chapter that the open and laparoscopic repairs are compared head to head, and I therefore feel that the title of the work is perhaps misleading. New data on keyhole hernia are emerging constantly and I would encourage the authors to maintain and update this title; it is suitable for both the surgeon in training and the serious devotee of hernia repair. If you are considering doing laparoscopic hernia repair and have not yet attempted one, buy this book first.

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Essentials of Surgery: Scientific Principles and Practice

L. J. Greenfield, M. W. Mulholland, K. T. Oldham, G. B. Zelenock and K. D. Lillemoe (eds). 279 × 211 mm. Pp. 835. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. £38.

This American textbook of surgery aims to summarize the essentials required for an understanding of the scientific principles of current surgical practice. The authors also claim to have produced a 'portable' textbook of surgery. However, at 28 × 22 cm, their text is too large to be carried around and it seems to be designed to be read at a study table. This criticism apart, the book is an excellent synopsis of the principles of current surgical practice.

The text is well laid out and clear. The first part of the book is devoted to scientific principles. There are excellent summaries of cytokines, inflammation, shock and critical care. Part two is devoted to surgical practice and the text is divided along traditional anatomical regional lines into head and neck, stomach and duodenum, liver, pancreas, etc. Each of these sections has a chapter on anatomy and physiology and follows with chapters devoted to surgical disease. This layout is commendable but the anatomy and physiology sections are, of necessity, rather concise summaries. The text describes current American practice and thus may not reflect surgical practice in the UK. For example, the chapter on pancreatitis describes the use of Ranson's criteria but makes no mention of the use of the Glasgow scoring system. This section highlights another common problem associated with medical textbooks: that of remaining up to date. Sadly, the

advice on nutritional supplementation and antibiotic prophylaxis in pancreatitis is obsolete. These minor criticisms apart, the book can be strongly recommended. The level of detail puts it into the competitive market for students sitting FRCS part B. Even though this is an area with a well defined reading list, the excellent basic scientific principles section makes *Essentials of Surgery* well worthy of consideration.

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Handbook of Anal Endosonography

C. I. Bartram and A. Frudinger. 221 × 144 mm. Pp. 79. Illustrated. 1997. Petersfield: Wrightson Biomedical Publishing. £24.50.

This monogram, in a simplified but comprehensive style, provides an adequate coverage of this new and developing technology, sparing the need for laborious manuals. A full account of the basic principles of ultrasonography, the equipment and technique of examination lay out the requirements. A description of the anatomy of the normal anal canal demonstrates the superiority of this technique in outlining ultrastructural detail and in recognizing morphological aberrations. The role of this investigation is principally in anal incontinence, trauma, sepsis and malignancy, and it is succinctly described and illustrated with endosonographs and histological sections. Clinicians, radiologists and radiographers interested in this field will find great value in this text. Although it appears simple and straightforward, to obtain the benefits of this investigation the authors' sharp acumen and mastership must clearly be matched.

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Breast Cancer

S. Haber (ed.). 229 × 151 mm. Pp. 178. Illustrated. 1997. London: Free Association Books. £14.95.

Since the introduction of the National Breast Screening Programme in the UK, the development of the multidisciplinary team has led to improvements in the diagnosis and treatment of patients with breast cancer. The Calman Report has also emphasized the role of the multidisciplinary team in improving outcomes in cancer treatment. This excellent little book highlights the not insignificant role of the psychologist/counsellor in the management of the patient and her family. After a brief overview of medical treatment of breast cancer, it explains the important inter-relationship between patients, clinician and counsellor. A comprehensive account of the psychological reactions to diagnosis and treatment follow; the post-treatment reaction and the effects of recurrent disease and terminal illness are covered fully. Emphasis is placed on the reaction of husbands, children and other significant family members. Special populations, such as high-risk groups and ethnic minorities, receive attention. Specific interventions and the role of support groups and group therapy are discussed adequately. The text is supported by a comprehensive list of resources and references. I believe this short volume is a valuable contribution to the holistic management of patients with breast cancer and should be read,

not only by students in psychology, but by all members of the multidisciplinary team. The authors are to be congratulated.

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Introduction to Organ Transplantation

N. S. Hakim (ed.). 224 × 160 mm. Pp. 252. Illustrated. 1997. London: Imperial College Press. Price not supplied.

This small multiauthor volume presents an overview of the history and current place of organ transplantation. It covers all of the intra-abdominal and thoracic organs presently being transplanted, in addition to bone marrow transplantation, skin transplantation and corneal grafting. Additional chapters discuss more general topics such as the human leucocyte antigen system, immunobiology, ethics, infection, donor management and immunosuppressive drugs. The future place of the rapidly developing field of xenografting is not addressed specifically but is touched on in a number of chapters. The book has a simple, uncontroversial approach to the topics covered without the exhaustive and often confusing inclusion of minutiae found in more elaborate texts. The various chapter authors do seem to have made a major effort to present their subjects simply, clearly and concisely. This volume will act as a useful introduction to organ transplantation for medical students, nursing and ancillary staff and non-transplant clinicians seeking to update themselves on the present situation in this ever-changing and evolving field. The major sections are adequately referenced for those wishing to pursue specific subjects in more depth, although the format and number of references is somewhat variable.

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Ambulatory Anesthesia and Surgery

P. F. White (ed.). 260 × 190 mm. Pp. 918. Illustrated. 1997. London: W. B. Saunders. £90.

Most surgeons practice day surgery, yet few have any understanding of the practical and managerial factors that make day surgery successful. This is, therefore, a timely book that offers an evaluation of day surgery practice from a multidisciplinary point of view for surgeons, nurses and managers. The principles and practice of modern day surgery, developed primarily in the USA and more recently in the UK, are carefully laid out. Book chapters are collected into sections covering organization, preassessment, surgery, pharmacology and anaesthetics, and patient recovery and discharge. There are also sections on paediatrics, the economic and legal aspects of day surgery, and a review of day surgery as practised around the world. Each chapter has been written by a different author, but all sections are overseen by contributing editors which adds fluency to the topics. The book has high production values and is illustrated liberally with useful tables, diagrams and photographs. Aside from its comprehensive range of day surgery practice, the book's other strength lies in its enormous collection of appropriate references. As day surgery practice is multidisciplinary, references can often be difficult to track down: this book lists almost all the seminal research in the field from accreditation of day centres to written patient information. I believe that this volume should be available in all day-surgery centres as a source of reference and to enable surgeons, anaesthetists and nurses to understand each other's roles in day surgery. Any surgeon involved in setting up or modernizing their

own day unit should also read the chapters on management and organization before starting.

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Therapeutic Endoscopy. Color Atlas of Operative Techniques for the Gastrointestinal Tract

N. Soehendra, K. F. Binmoeller, H. Seifert and H. W. Schreiber. 300 × 215 mm. Pp. 214. Illustrated. 1997. Stuttgart: Georg Thieme. DM298,00.

This book deals with flexible endoscopy of the gastrointestinal tract. In the preface the authors state that 'the artist's skills were decisive to the success of this book'. The illustrations are superb and carried out by an artist who understands her subject both anatomically and surgically. They are produced with great clarity and are easy to understand, with good legends. The English text also shows very little sign of the translator's work and is easy to read in natural English. This is not always achieved in other translated books. The chapters include an excellent one on methods of extracting foreign bodies from the gastrointestinal tract endoscopically, methods of bougienage, and balloon dilatation and oesophageal stent replacement. Further chapters then deal with performing gastrostomies and dealing with oesophageal varices. There are excellent illustrations on endoscopic retrograde cholangiopancreatography and spincterotomy, and dealing with pancreatic and biliary tract pathology. There is one chapter on polypectomy in the colon, and the book finishes with a chapter on mucosectomy for early cancer and endoscopic methods of treating Zenker's diverticulum. Each chapter is organised in the same way, giving details of the clinical condition, the indications for endoscopic treatment, instruments and technique, and the complications which may arise. The book is full of useful hints based on the experience of the authors. This attractive large volume is thoroughly recommended for anyone who has an interest in gastrointestinal endoscopy. It is probably also of interest to laparoscopic surgeons who are increasingly using combined internal and external approaches to abdominal problems.

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Abdominal Surgery of Infancy and Childhood

W. L. Donnellan, J. D. Burrington, K. Kimura, J. C. Shafer and J. J. White (eds). 286 × 222 mm (two volumes). Pp. 1300. Illustrated. 1996. Reading: Harwood Academic Publishers. £225.

The authors have adapted the same title as the original *Abdominal Surgery in Infancy and Childhood* by Ladd and Gross in 1941. Since then there have been many changes and the above title could mislead the casual browser as to the contents. Perhaps *Neonatal and Paediatric Abdominal Surgery* would more accurately describe the text. Volume 1 commences with several chapters on general management giving a good account of pain control, intensive care, laparoscopy and other general topics. However, in any textbook dealing with neonatal surgery, it is somewhat surprising that there is no chapter on antenatal diagnosis and intervention. Other chapters would have been of interest, such as transplantation, human immunodeficiency virus, non-accidental injury and ethics. There are other omissions in the text, for example, the chapter on endoscopy does not include bronchoscopy, and yet this is recommended before thoracotomy for oesophageal atresia and tracheo-oesophageal fistula. A vexing problem which paediatric surgeons, especially from developed countries, are increasingly faced with is recurrent abdominal pain associated with artefactual illness in childhood; this is not mentioned.

It is of interest to note that, although the authors are mainly from the USA, a few surgeons from other parts of the world have made contributions; none are from the UK or Australia. This work is easily readable and is generously illustrated with simple line diagrams, especially of the operative procedures. The text is enriched with a number of illustrations of radiological investigations. In relevant sections there is a good description of the embryology and pathophysiology. The numbering of the pages is different from the norm, since it lists chapters and pages for each section separately. Since this book does not contain any urology it will have limited use outside the developed world where the paediatric surgeon still has to deal with abnormalities of the urinary tract.

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Notices and announcements

25 February–1 March 1998

IX Asean Congress of Plastic Surgery
Penang, Malaysia

Information: M. Subramaniam,
Department of Plastic Surgery, Hospital
Ipoh, 30990 Ipoh, Perak, Malaysia

26–27 March 1998

3rd M62 Coloproctology Course
Manchester, UK

Information: J. Hill, Department of
General and Colorectal Surgery, Central
Manchester Healthcare Trust, Oxford
Road, Manchester M13 9WL, UK

20–22 April 1998

**The Paediatric Oesophagus. An
Interdisciplinary Symposium. Main
Topic: Gastro-Oesophageal Reflux
with a Special Interest in Alkaline
Reflux**

Izmir, Turkey

Information: O. Mutaf, Department of
Paediatric Surgery, Ege University Faculty
of Medicine, 35100 Izmir, Turkey

13–15 May 1998

**Association of Surgeons of Great
Britain and Ireland**

Edinburgh, UK

Information: Association of Surgeons of
Great Britain and Ireland, The Royal
College of Surgeons of England, 35–43
Lincoln's Inn Fields, London WC2A 3PN,
UK

20–24 June 1998

**Therapeutic Options for the Locally
Advanced Non-Small Cell Lung
Cancer**

Terme di Valdieri, Italy

Information: G. Buccheri, Scientific
Secretary, Ospedale A. Carle, I-12100
Roccavione (CN), Italy

12–17 July 1998

**XVII World Congress of the
Transplantation Society**
Montréal, Canada

Information: L. Felicissimo and Associates,
12449 rue Cousineau, Montréal, Québec,
Canada H4K 1P9

Instructions to authors

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Send three copies of original articles and other editorial matter to: The Editor, *The British Journal of Surgery*, Blackwell Science Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 0171 404 1831. Facsimile: 0171 404 1927. Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. State in the covering letter whether an abstract of the work has been published and give an appropriate reference on the title page. Disclose in the covering letter any potential or actual personal, political or financial interest you may have in the material, information or techniques described in the paper. The decision to publish or withhold such information will be made by the Editors. Acknowledge all sources of financial support for the work. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (BMJ 1994; 308: 39–42). When a paper has many authors (i.e. more than six), you may be asked to justify the inclusion of all names listed. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; 345: 668).

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Following final approval of articles, you will be asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. Do not justify. Please send us digital versions of your figures. Ideally, these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have

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Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* 1997; 336: 309–15, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. When quoting specific materials, equipment and proprietary drugs, state in parentheses the brief name and address of the manufacturer. Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript must have a 200-word structured abstract. Lengthy manuscripts are likely to be returned for shortening. The discussion in particular should be clear and concise and should be limited to matters arising directly from the results. Avoid discursive speculation. Randomized clinical trials should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles which are 600–900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Correspondence

The Editors welcome topical correspondence relating to articles published in the Journal. Letters should not exceed 250 words and should be typed double-spaced.

Typescripts

Manuscripts must be clearly reproduced with adequate space for editorial notes. Type or print the text on one side of sheets of A4 paper (210×297 mm) with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to you for recasting. Begin each section (abstract, introduction, patients and methods, results, and discussion) on a new page.

Title page

On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

Tables and illustrations

Submit three copies of all illustrations and tables. Type each table on a separate page with an appropriate brief title. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Submit radiographs, photomicrographs, etc. unmounted in the form of glossy prints, original transparencies or negatives. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s), indicate the top of the illustration. Include a measure of magnification of photomicrographs. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Include explanations of symbols and shading in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work give the original source in full. Obtain permission to use published work from the original author and the publisher before submission.

Abbreviations

Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5.7. Use a space and not a comma after thousands and multiples thereof, e.g.

10000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '*t* = 1.34, 16 d.f., *P* = 0.20'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ¹ or ¹⁻³. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in *Index Medicus* (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Oberic ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s); chapter title, editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

Leading articles

Advances in the surgical treatment of oesophageal cancer

Recent advances in diagnostic tools have greatly facilitated the early detection of gastric carcinoma in Japan and have helped improve the results of surgical treatment¹. However, most oesophageal carcinomas are at an advanced stage when detected and so many patients continue to die from this disease². Early detection is necessary to achieve better results in the treatment of all cancers but small oesophageal lesions, particularly intraepithelial cancers, remain extremely difficult to detect. Owing to the remarkable development and improvement in endoscopic techniques, as well as the present widespread use of endoscopic oesophageal biopsy under direct vision, early oesophageal cancer is beginning to be diagnosed with increasing frequency³.

Since 1985, whenever the mucosal surface appears abnormal, Lugol's solution has been applied here during the endoscopic examination, with biopsies taken from any suspicious areas⁴. A flat lesion usually has no colour change but it may be associated with a red spot, which can be observed clearly after Lugol staining as an unstained area. With this endoscopic method we have detected six epithelial carcinomas, 31 mucosal carcinomas and 75 submucosal carcinomas since 1987. This indicates that endoscopy with Lugol's solution and endoscopic biopsy are the most efficient diagnostic tools presently available for the detection of such small carcinomas of the oesophagus, many of which cannot be identified by radiography. In most instances, such lesions are detected incidentally during endoscopic procedures that are frequently performed for symptoms not directly related to the oesophagus. I believe that the application of Lugol's solution greatly aids diagnosis when a suspicious mucosal lesion is noted, when the margin of a lesion is unclear or when there is suspicion that a mucosal lesion may have been overlooked.

Nevertheless, the prognosis associated with oesophageal carcinoma remains one of the worst of the many types of digestive tract cancer. Investigators^{5–7} have reported, in Western countries, that the overall 5-year survival rate of patients with carcinoma of the oesophagus treated with current methods is disappointing, ranging from 8.8 to 21 per cent. As a result, carcinoma of the oesophagus remains one of the most discouraging areas in malignancy of the digestive tract.

From 1967 to 1996, 704 patients with carcinoma of the thoracic oesophagus underwent oesophageal resection in the Department of Surgery at Kyushu University Hospital. The patients were classified into three groups according to the date of operation. Group 1 consisted of 110 patients who underwent an oesophagectomy in the first 10-year period (1967–1976), group 2 consisted of 194 patients who had surgery from 1977 to 1986, and group 3 comprised 400 patients who had surgery from 1987 to 1996. The standard operative procedure comprised a subtotal oesophagectomy through a right thoracotomy, usually with reconstruction using the stomach through the antesternal route, combined with lymph node dissection⁸. To replace the resected oesophagus, the stomach, colon, jejunum, isolated jejunal segment or other conduit was used in 87, 6, 4, 1 and 2 per cent of the patients, respectively.

Complete removal of the primary tumour, including any metastatic lymph nodes, was achieved in 29, 39 and 62 per cent of the patients in groups 1, 2 and 3 respectively. The numbers now undergoing curative resection have recently increased remarkably. Over the years, various changes in treatment strategy have occurred, especially regarding the extent of the resection and the addition of a lymphadenectomy. As a result, most curative operations are now routinely completed with the addition of a cervical–thoracic–abdominal lymph node dissection⁹.

Resection and reconstruction of the oesophagus is probably associated with the highest mortality rate of any elective operation. The 30-day operative mortality rates were 11, 4 and 1 per cent in groups 1, 2 and 3 respectively; the increasing

expertise of the clinical team is demonstrated by the significant decrease in the mortality rate over time. The commonest causes of death within 30 days are pulmonary complications and cardiac failure. Age is no longer considered a contraindication to surgical treatment of the malignant oesophagus. Of the patients described above, 27 per cent were over 70 years old and 2 per cent were aged over 80 years at the time of surgery. The 30-day mortality rate for patients aged over 70 years has been only 3 per cent since 1987. Advanced age alone should not, therefore, be regarded as a reason for withholding operation.

The 5-year survival rates for all patients in groups 1, 2 and 3 were 16, 19 and 45 per cent respectively; long-term survival has clearly improved since 1987. The 5-year survival rates for patients having a curative resection in groups 1, 2 and 3 were respectively 31, 30 and 58 per cent. There are several reasons for such a remarkable improvement. The number of patients with early stage carcinoma has increased recently and surgeons have become more aggressive in resecting such disease. No patient with intraepithelial carcinoma or mucosal carcinoma had a recurrence within 5 years of surgery, whereas the 5-year survival rate of those with submucosal carcinoma was only 73 per cent. I consider that the criteria for early carcinoma of the oesophagus should include mucosal carcinoma as well as epithelial carcinoma, regardless of the presence or absence of lymph node metastasis; in addition, submucosal carcinoma should be excluded from the classification of early carcinoma of the oesophagus.

In conclusion, as a result of recent improvements, such as the early detection of carcinoma, safer operations and prolonged survival rates, surgery for carcinoma of the oesophagus should now be considered as the primary therapeutic approach of choice. The general pessimism toward patients with carcinoma of the oesophagus should be tempered by the knowledge that many such cancers can now be cured by the combination of timely diagnosis and adequate operative treatment.

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Leading articles

Rationing and surgery: setting boundaries

Rationing health care is now widely accepted as inevitable¹. It is not just inevitable today and in the UK; it is a part of all health care systems and will be for the foreseeable future. Even substantial increases in expenditure will not remove the need to ration health, that is, to deny beneficial interventions to people who need them.

Many governments around the world have started to grapple with this issue as it becomes increasingly visible to the citizens of their countries². In the American state of Oregon a commission was given the task of establishing a priority list of 'condition-treatment' pairs from which the state legislature would decide how many treatments it could afford to fund. Services that were funded, however, would be available for *all* the poor under the Medicaid programme rather than just a proportion. In New Zealand and the Netherlands state-sponsored committees were appointed to advise on how priorities should be set, and both countries set out to define a 'package' of services which would be available to all. This task proved too difficult and the emphasis shifted instead to developing national guidelines for local decision-making. Other countries have also started to make progress: in Sweden a government commission published an ethical framework on priorities and in Norway another framework was developed to reduce waiting lists. These developments have not resolved the issues they set out to address, but they do represent serious attempts by national governments to grapple with rationing and to confront their citizens honestly with what needs to be done. Unfortunately, UK governments have not yet followed this enlightened approach.

Why is not clear. It may be because talk of rationing often provokes fear and uncertainty. This, however, is almost always the result of semantic confusion. Rationing does not necessarily refer to wholesale denial of a service or treatment. It is about the inevitability of 'drawing a line' on the marginal improvements in health which can always be made. How many months, or weeks, of extra statistical life expectancy do we want to buy? When will that extra month of training no longer produce improvements in practice sufficient to justify the cost? When should we decide not to do the 'nth' diagnostic test? Should we screen ever-younger age groups for breast cancer to save a single life at huge expense? The simple fact is that 'the last drops of effectiveness are available at unaffordable costs'³. As well as those mentioned above, countries such as the USA, Canada, France and Germany, which spend far more on health care than the UK, are all grappling with the question of drawing the line and containing costs; this is rationing by another name^{4,5}.

Of course, the level of funding makes a difference. In the UK the relatively low levels of expenditure mean that rationing decisions (the benefits withheld) are more significant. But this does not necessarily imply a nation misguided; there is always the need to make a judgement about the relative benefit of what might be forgone in health terms against what might be gained in terms of other things of value in life. An extra year of life expectancy at enormous cost may not look particularly attractive next to an improvement in education for the youngest in society. Rationing does not imply underfunding⁶. Nevertheless, because countries do have such different funding levels it can be difficult to discuss a particular type of intervention, such as surgery, in universal terms. The difficult rationing decisions that surgeons and their teams have to make in the UK will be quite different from the decisions made elsewhere.

There is, however, one issue, as yet poorly understood and conceptualized, that can be seen to be relevant to all health care systems. It is also best exemplified by a particular type of operation. 'Cosmetic surgery' is a term which, to the lay person, sums up all that is trivial about the way in which a public health service allocates its resources. If people are dying through want of treatment why should anyone have their appearance enhanced? Plastic surgeons respond by reminding us that the psychological trauma undergone by some individuals is of the utmost

importance to them. Health economists for their part tell us to stop wasting our time, the quantity of resources in question is trivial and irrelevant to the real issue of how best to maximize the 'output' from a health care system.

However, liposuction, breast reduction and reduction rhinoplasty are procedures that, although apparently trivial, illuminate a fundamental issue of health care systems. What is the limit to which the skills and expertise of clinical practitioners must be subject in practising their craft? This is not a limit in terms of time or other resources. It is a limit to the kinds of benefit that these individuals are able to provide. It is quite clear that highly skilled people, such as plastic surgeons, making the most of their particular skills in aesthetic surgery, could benefit me in a wide range of ways; they have certainly worked wonders on Hollywood stars such as Cher and Tina Turner. But is this the sort of benefit which the National Health Service (NHS) in the UK wants to buy?

It is worth reformulating this issue in terms of clinical effectiveness. It could be argued that anything that is not outrageously expensive and which is demonstrated to be effective should be offered through the NHS. But something can be effective (it achieves what it set out to achieve) and yet not achieve that which the NHS desires. By making this point I do not want to suggest that all cosmetic surgery is unnecessary; if the benefit is to reduce psychological trauma the NHS may indeed wish to provide it, but there has to be a limit to what surgeons (and all other health care practitioners) can do. They are highly skilled people dealing with basic desires and wants, and they often have the potential to provide the kinds of benefit which are simply not relevant to a *health* service.

It is extremely difficult to establish this boundary, although at least one attempt has been made⁷. Furthermore, it should also be clear that the problem applies just as much to physiotherapists providing manipulative therapy (when does a massage improve health status and when is it merely pleasant?), family doctors giving advice (where do we draw the line between advice that promotes health and that which is purely social?), and nurses providing long-term care (when does long-term nursing care for the elderly become something a health service should provide?). All these things do good, but which of the good things are relevant to the NHS?

The question applies to all health care systems, as is immediately apparent if one considers a private health insurance system. Even the most comprehensive insurance package will not allow entirely free rein to medical practitioners. The boundaries (the range of available treatments) will be carefully defined. In fact, the UK is probably lagging behind other similar countries in its ability to confront this issue. The NHS, operating differently from the social insurance systems of our European partners, has not tended to draw attention to this problem. Still, it will not go away. The example of liposuction may seem trivial, but it is analogous to the heated debate about NHS funding of long-term care; the latter has been proposed as the subject of a Royal Commission.

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Review

Management of faecal incontinence following obstetric injury

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Background Faecal incontinence is common in women and the major aetiological factor is childbirth. Increasing numbers of women with faecal incontinence are presenting to surgical clinics.

Methods A literature review was performed on Medline database for English language publications on obstetric injury. The incidence, presentation, assessment and treatment of faecal incontinence following obstetric injury were evaluated.

Results and conclusions Third-degree tear occurs in association with less than 1 per cent of vaginal deliveries, but occult sphincter injury occurs at one-third of deliveries and may be significant in later life. Incontinence may result from sphincter damage or nerve injury, or both. Risk factors for these injuries can be identified. Clinical evaluation, anorectal physiology and endoanal ultrasonography allow accurate planning of subsequent surgery. Overlapping anterior anal sphincter repair provides symptomatic control of continence in 80 per cent of patients. Repair of an acute anal sphincter injury after a third-degree tear is controversial and a defined policy should be agreed between obstetric and colorectal teams.

Loss of voluntary control of stool is a distressing condition. Faecal incontinence is a physically and psychologically disabling symptom with major social implications for the affected individual. At least 5 per cent of healthy people admit to incontinence at some stage if soiling is included^{1,2}. Even if only involuntary loss of stool is considered, the prevalence is between 0.5 and 1.5 per cent in the general population. The prevalence of faecal incontinence increases with age, and in women aged over 65 years it reaches 13 per 1000³. As many as half the patients in psychogeriatric wards are regularly incontinent of faeces and this is often accompanied by urinary incontinence.

Faecal incontinence affects not only the elderly population. The incidence in 45-year-old women is eight times higher than that in men of a similar age and this is likely to be due to obstetric factors⁴. Damage to the perineum is a common complication of vaginal delivery and in a proportion of patients this may lead to faecal incontinence. As many as 13 per cent of women having their first vaginal delivery develop a degree of incontinence (usually to flatus) or urgency⁵.

Incontinence following obstetric injury is important for a variety of reasons. The number of women presenting to surgical clinics with such symptoms is increasing. Furthermore, obstetric injuries and their sequelae are responsible for an increasing number of medicolegal cases. The assessment and management of this problem has advanced considerably over the last few years, largely as a result of the introduction of endoanal ultrasonography. This review discusses the incidence, presentation, methods of assessment and treatment options available for women presenting with faecal incontinence secondary to obstetric injury.

Maintenance of continence

Continence is dependent on a number of inter-related factors. These include rectal compliance, rectal sensation, anal sensation and an intact rectoanal inhibitory reflex. In addition, the internal anal sphincter (IAS) develops spontaneous tone due to its own myogenic activity⁶ and extrinsic adrenergic properties⁷; this provides a natural barrier to the involuntary loss of stool. The IAS is responsible for 50–85 per cent of resting tone, with the external anal sphincter (EAS) and anal cushions contributing the remainder^{8,9}. The EAS, puborectalis and other muscles of the levator ani form a skeletal muscle complex innervated by the pudendal nerves and inferior rectal nerve. The EAS and pelvic floor muscles maintain resting tone as a result of a reflex arc involving stretch receptors in the levator ani and anal sphincters, through an afferent neurone to the cauda equina and an efferent motor neurone to the muscles. The EAS and levator ani also have a predominance of type I muscle fibres, making them more adapted to tonic activity. Disruption of the IAS leads to passive faecal incontinence (loss of faeces without the patient's awareness). Dysfunction of the EAS results in urge incontinence due to the patient's inability to suppress defaecation¹⁰.

Aetiology of incontinence following childbirth

The aetiology of faecal incontinence is complex but following childbirth can be broadly classified as traumatic sphincter injury or nerve injury. Non-obstetric causes of incontinence must be excluded before treatment. Such causes of faecal incontinence are listed in *Table 1*.

Nerve injury

In 1877 Gowers¹¹ described the rectoanal inhibitory reflex in which the IAS relaxes transiently in response to rectal distension. Duthie and Bennett¹² demonstrated that the

Table 1 Non-obstetric causes of faecal incontinence

Incontinence with normal sphincters
Severe diarrhoea
Faecal impaction
Poor rectal compliance
Inflammatory bowel disease
Rectal tumour
Extrinsic compression
Fistula
Dementia or learning impairment
Incontinence with abnormal sphincters
Direct sphincter injury
Surgical
Traumatic
Sphincter neuropathy
Upper motor neurone lesion
Cerebral (tumour, stroke, trauma)
Spinal (demyelination, tumour)
Lower motor neurone lesion
Cauda equina lesions
Diabetes
Pelvic tumour
Demyelination
Congenital anomalies
Rectal prolapse

rectoanal inhibitory reflex allows rectal contents to come into contact with the upper anal canal which has a rich innervation of free and organized sensory nerve endings¹³. This is thought to be important in fine control of continence and allows differentiation between liquid and flatus. Sampling, the point of equalization of rectal and anal pressures, occurred in 16 of 18 control patients but in only one-third of patients with faecal incontinence¹⁴. Reduction in anal sensation and defective sampling are likely to be important in the pathogenesis of faecal incontinence. Furthermore, impaired anal sensation has been demonstrated following both normal vaginal and instrumental delivery, compared with sensation in controls or women delivered by caesarean section¹⁵. However, at 6 months after childbirth there was no difference between these groups.

For many years injury to the nerves of the pelvic floor was thought to be the main cause of incontinence^{16,17}. Parks *et al.*¹⁸ noted increased fibrous connective tissue and degenerative changes in EAS muscle fibres in 24 women with faecal incontinence. It was suggested that incontinence occurred secondary to denervation following nerve injury during childbirth. The advent of pudendal nerve terminal motor latency (PNTML) tests allowed the demonstration that many patients with incontinence had prolonged PNTML, indicating nerve damage, although a proportion had PNTML within normal limits.

More recent studies have demonstrated that the IAS is also affected by denervation in patients with incontinence¹⁹. Degenerate muscle cells, increased fibrous tissue and reduced sensitivity to agonists *in vitro* have been demonstrated²⁰. In a study of 128 women during pregnancy and after delivery, PNTML was slightly prolonged after delivery, indicating a degree of nerve damage²¹. Sixteen per cent of women had prolonged PNTML after delivery but only one-third of these remained prolonged at 6 months. Only a small proportion of women, therefore, develop a long-term neural deficit. Other work has suggested that the damage to the pudendal nerves persists at 5 years²². Age is an important factor when assessing anorectal function. PNTML increases with age and the IAS generates a lower pressure

with increasing age²³. About 10 per cent of women presenting with idiopathic incontinence have no identifiable structural defect and in this group nerve damage appears to be the only aetiological factor. The majority of patients, however, have a history of some form of injury involving the IAS, EAS or both, and those sustaining the greatest trauma during childbirth are likely to have both nerve and muscle damage²⁴.

Sphincter damage

The assessment of sphincter injuries has been revolutionized by the development of endoanal ultrasonography²⁵. An instrument containing a small rotating ultrasound probe is inserted into the anal canal to enable identification of the IAS and EAS (Fig. 1). Cadaveric studies have shown a close correlation between ultrasonographic images and anatomical structures^{26,27}. Sphincter defects can be identified accurately to allow planning of

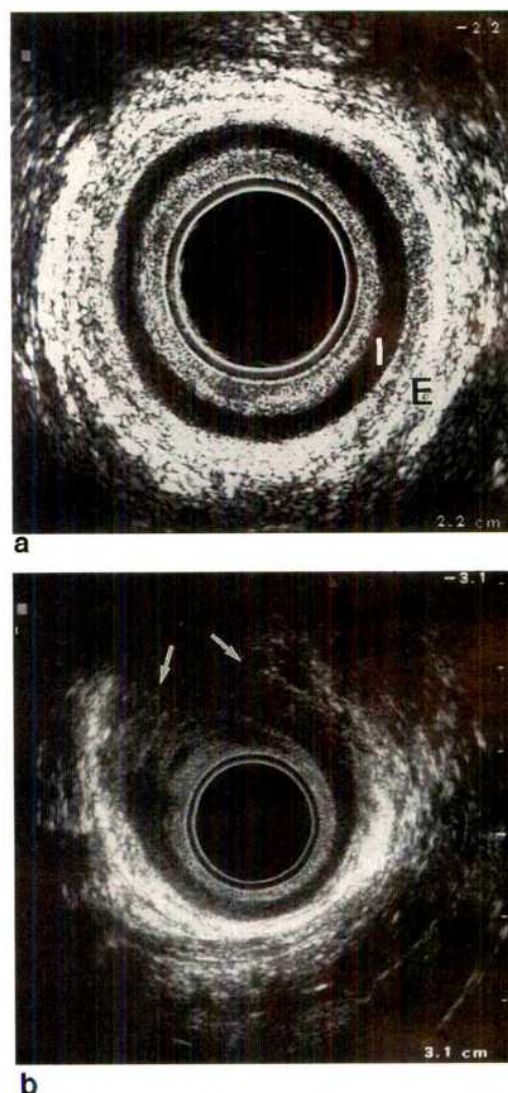


Fig. 1 **a** Normal endoanal ultrasonographic scan. Anterior is at the top. The internal anal sphincter (I) appears as a dense hypoechoic ring and the external anal sphincter (E) as a heterogeneous thick ring. **b** Endoanal ultrasonographic scan showing an anterior defect in the external anal sphincter (arrowed), extending into the internal anal sphincter

subsequent surgery^{28,29}. Transvaginal ultrasonography also provides accurate images of the sphincters and anterior defects in the upper, but not the lower anal canal³⁰. Endoanal ultrasonography is quick to perform and comparatively cheap³¹.

Large studies have assessed the incidence of third-degree tears, defined as a laceration of the perineum involving the anal sphincter with or without involvement of the anorectal mucosa³²⁻³⁴. Between 0.5 and 1 per cent of women delivering vaginally sustain a third-degree tear on clinical assessment; risk factors are forceps delivery, primiparous delivery, high birth-weight (more than 4 kg), occipitoposterior presentation and prolonged second stage of labour. While the overall incidence of faecal incontinence is 0.04 per cent, after a third-degree tear it is 7 per cent, with a further 12 per cent incontinent to flatus.

While forceps delivery increases the risk of injury to the sphincter complex, no third-degree tears occurred in a series of 351 vacuum extractions³³. Despite the increased risk of forceps delivery only 3 per cent of these deliveries result in a third-degree tear³⁴. Another study compared different instrumental deliveries with unassisted vaginal delivery³⁵. Patients were matched in all respects and choice of instrument depended on operator preference. Sonographic sphincter defects were identified in 81 per cent of forceps deliveries, compared with 21 per cent of vacuum extractions and 36 per cent of unassisted deliveries. Furthermore, 38 per cent of women with forceps deliveries experienced defaecatory symptoms, compared with 12 per cent of those with vacuum deliveries and 4 per cent with unassisted births.

A randomized prospective study of 407 episiotomies demonstrated that midline episiotomy was associated with an increased risk of sphincter damage compared with mediolateral episiotomy³⁶; other studies have failed to demonstrate any difference. In any event there is increasing evidence that mediolateral episiotomy does not protect against third-degree tear, with as many as 74 per cent of women with a tear having had an episiotomy compared with 28 per cent of those without a tear³⁴. Another study has similarly shown an apparently higher incidence of episiotomy in women who sustained a third-degree tear, although once corrected for parity and birth-weight there was no difference between the two groups³². Care must be exercised in interpreting these results because the proportion of patients who may have developed a third-degree tear without an episiotomy is unknown.

Sultan *et al.*⁵ showed that 35 per cent of primigravidae who delivered vaginally developed a sonographic defect which persisted at 6 months. Women with sphincter defects had lower resting anal pressures than those without, and all those with incontinence had defects. Only 4 per cent of multiparous women developed new sonographic defects, although 40 per cent had existing sphincter damage before delivery. There was no correlation between nerve latency measurements and the development of bowel symptoms. Reduced squeeze pressures have also been demonstrated in patients with tears and these persisted 6 months after the injury.

The reported incidence of third-degree tears clearly depends on the method of assessment. Large studies have based the assessment on clinical evaluation but endoanal ultrasonography has identified a much larger proportion of women with sphincter defects. The significance of these occult injuries has not been fully established and not all of these women become incontinent as a result of the defect.

However, the occult injury may predispose to incontinence in later life and it is possible that other factors such as hormonal changes at the menopause are important in altering the balance.

Presentation and clinical assessment

Women presenting with incontinence related to childbirth fall into three categories. First, there are those who present some time after delivery, often in middle age. Second, a group exists who have had a tear repaired acutely but present with incontinence within the first year, usually due to disruption of the repair. The third group includes those in whom sphincter disruption is noted at the time of delivery and in whom a management plan can be developed immediately. This final group represents an acute problem and will be discussed separately.

For women who present some time after delivery a careful clinical history is essential. It is important to establish the degree and frequency of incontinence and the effect on quality of life. Assessment should include questions on the patient's ability to perform domestic and social activities, whether or not she is able to go on holiday and the impact on sexual activity. The use of pads and the need to change underwear are also good indicators of severity of incontinence. A scoring system allows a more objective evaluation of function before and after repair, and permits comparison with other series^{37,38}. A detailed obstetric history is vital and it should be established whether previous repairs were complicated by infection or wound breakdown. Other potential causes of incontinence should be excluded.

Examination of the perineum identifies scars and allows assessment of the anal margin. Digital examination by a specialist has been shown to compare favourably with manometric assessment of anal sphincter function³⁹. Perineal soiling should be noted, and sigmoidoscopy and proctoscopy aid in excluding organic conditions such as neoplasia or proctitis.

Anorectal physiology

Simple clinical assessment should be combined with more sophisticated techniques. A combination of tests is available to assess the various components involved in the maintenance of continence (Table 2). While endoanal ultrasonography has become the first-line tool in the investigation of sphincter injury, its use may be complemented by other tests of anorectal physiology.

Manometry permits measurement of the anal canal length, and the resting and squeeze pressures. A number

Table 2 Methods of assessment of anorectal incontinence

Method	Utility
Clinical	
Inspection	
Digital examination	
Endoanal	Good definition of anatomical structures and defects
ultrasonography	
Anorectal physiology	
Manometry	Allows assessment of contribution of the internal and external sphincters to overall sphincter pressure
Pudendal nerve latency	Assesses pudendal nerve damage
Anal canal sensation	

of methods is available, the most widely used being a multichannel catheter perfused with water. Balloon techniques do not give a radial profile and may be affected by the balloon itself. Women with incontinence following obstetric injury have reduced resting and squeeze pressures. Further studies using an intrarectal balloon allow the rectal capacity, sensitivity and rectoanal inhibitory reflex to be assessed.

Measurement of PNTML is an assessment of pudendal nerve function. The evoked response of the EAS is observed following transrectal stimulation of the pudendal nerves. PNTML measurement is important before embarking on sphincter repair, as a prolonged value is a prognostic indicator of poor long-term functional success after surgery^{40,41}. Normal latencies do not exclude nerve damage because only the fastest conducting fibres are recorded. In addition, there is considerable anatomical overlap of pudendal innervation on both sides of the EAS⁴². Assessment of anal canal sensation should also be made, this is impaired in the upper canal in women who sustain sphincter damage at delivery¹⁵.

Until the advent of endoanal ultrasonography, concentric-needle electromyography (EMG) was used to map the EAS by quantifying motor unit potentials in affected areas. Characteristic changes occur following injury, denervation and partial reinnervation⁴³. Although further information on reinnervation may be obtained from single-fibre EMG, this is painful for the patient and has little effect on management. Endoanal ultrasonography has rendered the need for EMG largely superfluous⁴⁴.

Treatment

The importance of a detailed history becomes relevant when deciding on the best treatment for a particular individual. Minor degrees of incontinence are common, especially in elderly women, and the majority of these patients can be managed conservatively with satisfactory results. Major disruption of the sphincters may lead to more severe symptoms and in this situation surgery is usually required.

Conservative therapy

Dietary manipulation is the first step in treatment of minor degrees of incontinence. A low-residue diet reduces the amount of fluid in the stool, which can then be more easily controlled by the sphincters. Antidiarrhoeal agents such as codeine phosphate or loperamide are useful as additional agents if dietary manipulation alone is unsuccessful. Loperamide has a constipating effect and also increases IAS tone^{45,46}. Maintaining an empty rectum with the use of regular enemas and inducing planned bowel movements may help further.

Pelvic floor exercises, involving contraction of the pelvic floor muscles at regular intervals throughout the day, have been shown to be of benefit in relieving symptoms of seepage⁴⁷, but objective data supporting this method of treatment are lacking. Recent interest has been shown in biofeedback as a method of improving continence⁴⁸. A sensing device connected to a transducer monitors EAS activity and patients are encouraged to improve the response, which gradually becomes automatic. Careful patient selection is vital and depends on factors such as motivation, ability to understand instructions, presence of some rectal sensation and the ability to contract the EAS voluntarily. Postobstetric incontinence is seldom due to

nerve damage alone and, consequently, biofeedback may be of little help in the majority of patients with sphincter disruption. Nevertheless it has recently been shown that successful outcome is independent of manometric pressures⁴⁹. Although small observational studies report some success⁵⁰, the results of randomized controlled studies are awaited.

Surgical treatment

Patients with a defect in the EAS are suitable for surgical repair as the remaining sphincter retains the ability to contract. Although plication procedures have been used for neurogenic faecal incontinence, they have little role in the management of sphincter defects, for which a direct repair is more appropriate.

Apposition technique. This involves mobilization of the EAS, excision of scar tissue and direct end-to-end suturing of the muscle. It is an attractive option because of its simplicity, but results are poor. This is likely to be because of muscle retraction and disruption of the anastomosis. A recent study reported satisfactory continence in 31 of 40 patients⁵¹ but the operation has largely been replaced by the overlapping repair.

Overlapping anterior sphincter repair Originally described by Parks and McPartlin⁵², the overlapping repair has been modified and has now gained widespread acceptance. Scar tissue is preserved and dissection continued back until viable EAS muscle is identified. A nerve stimulator aids identification of the EAS. The overlap is created with the fibromuscular ends; this provides bulk anteriorly in the region of the perineal body and increases the area of contact, reducing the risk of suture disruption. In addition, imbrication of the IAS may be performed, but this is often difficult due to fragmentation of the muscle and there are no data to suggest it is effective.

Preoperative preparation should include urinary catheterization, administration of antibiotics and full bowel preparation. Formation of colostomy to divert the faecal stream is not usually required^{53,54} but trials are in progress to assess functional outcome in those with and without a defunctioning stoma. Defunctioning may be of benefit in patients undergoing recurrent sphincter repair but, again, there is a lack of data. After operation stool softeners should be given to prevent straining and possible disruption of the repair.

Most studies of anterior sphincter repair include patients with defects due to non-obstetric causes, such as fistulotomy. Satisfactory results have been reported in 70–80 per cent (Table 3). Good results reflect continence

Table 3 Results of overlapping anterior anal sphincter repair

Reference	Year	No. of patients	Obstetric injury (%)	Results excellent or good (%)
Sitzler and Thomson ⁵⁴	1996	31	65	74
Oliveira <i>et al.</i> ⁵⁵	1996	55	100	71
Felt-Bersma <i>et al.</i> ⁵⁶	1996	18	55	72
Engel <i>et al.</i> ⁵⁷	1994	55	100	79
Londono-Schimmer <i>et al.</i> ⁵⁸	1994	94	60	50
Fleshman <i>et al.</i> ⁵⁹	1991	55	87	72
Jacobs <i>et al.</i> ⁶⁰	1990	30	100	83
Laurberg <i>et al.</i> ⁴⁰	1988	19	100	47

to solids and liquids, but control of flatus is more difficult. This is likely to reflect injury to the IAS, which is often difficult to repair owing to muscle fragmentation at the time of surgery. There is good correlation between subjective functional improvement and objective improvement in physiological scores⁵⁵. Prolonged PNTML is a predictor of poor functional outcome⁶¹ and other factors, such as previous attempts at repair or length of pre-operative symptoms, may also affect success. Increased age does not preclude a good result^{55,57}.

Acute presentation of third-degree tears

This represents a problem in its own right, with other factors such as the newborn child to be considered. Most sphincter injuries are recognized at the time of delivery and the majority are sutured in the delivery suite, often by junior medical staff who have a poor understanding of anal anatomy⁶². Often an end-to-end repair is performed and primary repair of third-degree tears is, therefore, frequently inadequate, with up to 50 per cent of women experiencing some degree of incontinence and 85 per cent having subsequent sphincter defects identified on ultrasonography³³.

A further problem in the acute setting is that the tissues are often swollen, bleeding and contaminated with liquor or, occasionally, faeces, making identification of the muscle difficult. The optimum timing of repair is not known. Options include immediate repair in the delivery suite, repair the following day (allowing the oedema to settle), repair 2 weeks later, and waiting a few months for scar tissue to form before undertaking elective repair. Future studies may determine which of these provides the best results. Similarly, there are no studies evaluating who is likely to offer the best hope of repair. Whether these injuries are better dealt with by colorectal surgeons is unknown, but a defined local policy should be agreed with the obstetric team, and follow-up in the colorectal clinic 3 months after delivery has been advocated³⁴. Dedicated obstetric follow-up clinics for women with third-degree tears have also been established.

Immediate repair by the colorectal surgeon in the delivery suite may be hampered by unfamiliar equipment and staff. If the operation is to be performed in a colorectal unit, adequate provision must be made for both mother and baby in the early postnatal period. The use of a stoma in this group is not mandatory but, in a proportion of patients with added infection or a major tear involving the rectal mucosa, the authors advise this step.

The development of a third-degree tear not only prolongs hospital admission at an important stage of the mother and baby's relationship but may have longer-lasting consequences. Transient faecal incontinence after a third-degree tear is associated with an increased risk of anal incontinence after subsequent vaginal delivery⁶³. A caesarean section for future deliveries should be recommended to these women.

Failure of sphincter repair

Wound infection may occur in up to 24 per cent of patients and wound disruption may follow primary repair in about 10 per cent⁶⁴. Two-thirds of the latter require further surgery for complications, such as rectovaginal fistula or incontinence. Poor functional results following repair are associated with persistent sphincter defects⁶⁵. Repeated sphincter repairs may be attempted but finding

viable tissue becomes increasingly difficult with each operation. Encirclement procedures, similar to those used for rectal prolapse, have been attempted but results are universally poor. Recently, artificial sphincter implantation has been tried. Although early results are encouraging⁶⁶, the long-term outcome is still to be established.

Repair by skeletal muscle transposition has also been advocated; the commonest muscles used are the gluteus maximus and gracilis. Gracilis muscle transposition was first described by Pickrell *et al.*⁶⁷ and involves wrapping the gracilis muscle around the anal canal and suturing it to the contralateral ischial tuberosity. Small series report encouraging results but improvement in resting or squeeze pressures has not been observed. Segments of gluteus maximus may also be used and successful results associated with increased squeeze pressures have been reported. Stimulation of gracilis to convert the muscle fibres from type II fast-twitch fibres to fatigue-resistant type I slow-twitch fibres may improve outcome^{68,69}. However, this is a major undertaking which usually requires three separate operations, and results remain mixed.

Construction of an end colostomy may be indicated. Some women will already have experienced a temporary diverting colostomy if they have undergone recurrent sphincter repair. Many find that the colostomy can be more easily managed than an incontinent anal sphincter, allowing a dramatic improvement in quality of life.

Conclusion

Anal sphincter damage following vaginal delivery is common and many women have occult sphincter injuries that may predispose to faecal incontinence in later life. If instrument-assisted delivery is needed, vacuum extraction appears to be associated with a reduced incidence of sphincter injury than forceps delivery. The role of episiotomy in reducing the incidence of third-degree tear has not been established and primary repair of third-degree tear is associated with a high failure rate. The authors advocate follow-up and assessment using the equipment available in many colorectal departments for women who sustain a third-degree tear, regardless of who performed the primary repair.

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Announcement

Referee performance

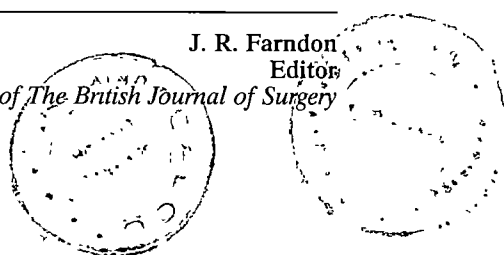
The British Journal of Surgery is highly dependent upon its panel of referees for assessment and evaluation of papers submitted. The Journal currently receives 1300–1500 papers per annum and, by the judgement of its referees, rejects 70–80 per cent of these. An editorial policy is to try and give priority to papers that describe novel and scientifically meritorious surgical investigations. The new referee sheets attempt to determine these facts in an easier way.

In an attempt to improve the quality and turnover for papers the editors have recently increased the demands upon referees. There is a request that assessment of a paper by a referee is turned around within 3 weeks. If no response is received within 3 weeks, despite geographic location of referees, a chase letter or prompt reminder is sent to the referee. The result of this more stringent driving policy has been that referees have responded more expeditiously. If we examine the turnover between receipt of a manuscript to notification of rejection these times have changed significantly (time to acceptance is erroneous for the purposes of this exercise as this length of time is as much dependent on the time taken by authors to resubmit a paper as the time taken by the referee to review it). Between the years 1993 and 1996 the response rate was an average of 80 days; last year this came down to 54 days.

The editors of the Journal and the officers of the Society wish to acknowledge the enormous debt owed to referees who support the Journal in a spirit of commitment and loyalty which goes beyond the call of duty. The editors, Council and Journal remain within the debt of the referees who provide such loyal and committed service. It is hoped that the gratitude will be duly declared at or around the time of the millennium!! Readers and contributors should be aware of the enormous unpaid contribution from referees which underpins the quality and progress of the Journal. We are grateful to surgeons, clinicians and scientists who support the Journal in such an admirable way. We are particularly grateful for the loyal support which ensures progressive improvement in the quality and performance characteristics of the Journal. The editors thank you for your support during 1997 and look forward to your continued loyalty and commitment during 1998. The year 2000 is not too far away!

J. R. Farndon
Editor

on behalf of the editorial team and Council of *The British Journal of Surgery*



Review

Adjuvant therapy for resectable rectal and colonic cancer

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Background Recurrence of rectal and colonic carcinoma remains substantial despite apparently curative surgery. Adjuvant therapy has been applied to improve prognosis.

Methods This review evaluates the use of adjuvant therapy in the management of resectable rectal and colonic carcinoma. It assesses critically the evidence supporting the addition of radiotherapy, chemotherapy, chemoradiotherapy and other treatment modalities to optimal surgery.

Results In the case of rectal tumours, preoperative is more effective than postoperative radiotherapy; it can significantly reduce the incidence of local tumour recurrence. A number of trials have tended towards showing a survival advantage and a recent large randomized trial has shown a significant improvement in survival in patients with Dukes C tumours. Postoperative chemoradiotherapy is associated with a survival benefit and is standard therapy in the USA, although it is associated with increased toxicity. The effectiveness of preoperative chemoradiotherapy is currently being investigated. Postoperative fluorouracil-containing chemotherapy has resulted in a survival advantage in patients with Dukes C colonic tumours; such therapy may be administered either systemically or intraportally. The evidence of benefit with rectal tumours is more limited. Immunotherapy has been studied to a limited extent and the use of a tumour-directed monoclonal antibody has produced a survival advantage in a single trial.

Conclusion Preoperative radiotherapy and postoperative chemoradiotherapy can produce a survival advantage in patients with Dukes C rectal carcinoma and reduce local recurrence. Postoperative fluorouracil-containing chemotherapy can produce a survival advantage in those with Dukes C colonic cancer. The optimal use and combination of adjuvant therapy remains uncertain.

Colorectal carcinoma is a common tumour, with over 28 000 new cases in the UK in 1987¹. It caused over 19 000 deaths in 1990², 6000 of these from rectal carcinoma; prognosis following curative surgery for colorectal carcinoma barely improved over the previous three decades³. The pattern of recurrence differs between colonic and rectal tumours. Colonic tumours usually recur in the form of disseminated disease which may be accompanied by local disease, whereas rectal tumours usually recur locally without disseminated spread^{4–6}. For rectal carcinoma, the incidence of local recurrence following curative resection ranges between 2–6 per cent⁷ and 32 per cent⁸, and a review of local recurrence following curative surgery indicated a median of over 15 per cent⁹. The relatively high incidence of recurrence and disappointing prognosis following apparently curative resection of colorectal carcinoma has stimulated research into the optimal management, with the aim of improving survival while minimizing the morbidity associated with treatment. Surgery remains the primary treatment and, while this has become more refined, there is still debate over the specific procedure to maximize cure and minimize morbidity^{10,11}. The role of adjuvant therapy (radiotherapy and chemotherapy) in the management of resectable tumours remains an area of uncertainty.

The aims of surgery are to excise the tumour and regional lymphatic drainage completely with clear resection margins, to preserve function with avoidance of

a colostomy, and to minimize collateral damage. Surgical resection of colonic carcinoma has undergone far less debate than that of rectal carcinoma. Easier access outwith the depths of the pelvis, defined lymphatic drainage adjacent to the arterial supply, and well perfused tissues (in the absence of obstruction) allow resection of the colonic tumour with its draining lymphatics and primary anastomosis of the bowel. Extended bowel resection provides no additional benefit¹².

The management of rectal carcinoma was revolutionized at the turn of the century with the description of abdominoperineal resection of the rectum by Miles¹³. This concurred with the principles of *en bloc* resection of potential pathways for lymphatic spread described by Moynihan¹⁴ and remained the 'gold standard' treatment of rectal carcinoma until the past decade. The necessary margins of resection have become modified following careful histological studies. It has been demonstrated that distal intramural spread below the tumour is rare^{15,16} and that clearance of as little as 1 cm may be adequate⁷. Combined with the introduction of mechanical stapling devices¹⁷, this has contributed to a significant increase in the proportion of sphincter-saving operations performed and a reduction in abdominoperineal resection. This trend to less mutilating surgery has not been accompanied by an increase in recurrence or decrease in survival. Although there are two reports of increased local recurrence after anterior resection compared with abdominoperineal resection^{18,19}, most studies^{20–24} fail to show any difference in terms of local recurrence between the two operations and this is reflected in similar rates of 5-year survival after surgery^{20,21,24–27}.

The importance of lateral clearance was demonstrated by Quirke *et al.*²⁸, who showed that even with careful surgical technique it was possible unknowingly to leave microscopic tumour deposits at the lateral resection margins and that extension of tumour to the lateral resection margin was related directly to recurrence²⁹. Heald *et al.*³⁰ demonstrated the presence of tumour deposits in the mesorectum distal to the tumour and that total mesorectal excision, performed in the appropriate plane³¹, reduces involvement of the lateral margin and results in local recurrence rates as low as 4 per cent³². Other studies^{33,34} have confirmed the benefit of total mesorectal excision in the reduction of local recurrence, and the presence of distal mesorectal deposits have been shown to increase the risk of both local and distant recurrence³⁵. None of these studies, however, contains any control data for comparison.

Surgical resection is intended to remove the lymphatic pathways along which the tumour may spread; rectal lymphatic drainage has been described as predominantly axial but also lateral³⁶. Japanese groups³⁷ have reported lateral lymphatic involvement beyond the mesorectum in 36 per cent of patients with low rectal cancer, and have noted lateral lymphatic spread in the absence of mesorectal involvement, the spread having 'skipped' the mesorectum. Extended surgical lymphadenectomy has been performed to address this problem but, although some control data are available, none of the available studies was randomized. Four earlier studies³⁸⁻⁴¹ demonstrated no improvement in 5-year survival while three later studies^{37,42,43} demonstrated a significant survival advantage. The incidence of urinary dysfunction and impotence was significantly increased by radical surgery. More recent work has concentrated on nerve-sparing resection (if possible) while ensuring tumour clearance⁴⁴. Alternative surgical procedures other than anterior resection and abdominoperineal resection may be used, but these are at present restricted by tumour stage or are limited to clinical trials. Local excision of rectal tumour should be limited to small stage T₁ tumours which are well or moderately differentiated⁴⁵ and which carry a low risk of recurrence.

Variability between surgeons should always be considered when assessing any operation. A number of studies^{18,46} have confirmed varying local recurrence rates between surgeons after resection for colorectal cancer, ranging from 0 to 21 per cent; even with increased surgical specialization, variability remains. The poor overall prognosis following 'curative' surgery for both colonic and rectal carcinoma has encouraged the use of adjuvant therapy, both local and systemic, in an attempt to reduce local and distant recurrence, and improve disease-free and overall survival rates.

Radiotherapy

The concept of radiotherapy for rectal cancer is not new⁴⁷ but still remains an area of uncertainty. Its role in the management of colonic cancer is limited and, although one report has shown a reduction in local recurrence of colonic carcinoma in selected groups with the addition of radiotherapy⁴⁸, this was a retrospective study with historical controls. Studies of adjuvant radiotherapy have concentrated on rectal carcinoma where local recurrence is a greater problem. Endocavity radiotherapy has been administered as adjuvant therapy⁴⁹ but has been investi-

gated to a greater extent as primary treatment for early rectal tumours^{50,51}. The trials are small and unrandomized and, as an adjuvant therapy, the use of such radiotherapy is very limited. External beam radiotherapy is the usual method of administration and it may be used before or after surgery with a different rationale in each case. Combined preoperative and postoperative radiotherapy has been used⁵² but this was associated with a high morbidity rate. Intraoperative radiotherapy has been reported^{53,54}, but this has been used for irresectable or recurrent rectal tumours rather than in the primary management of resectable neoplasms; it has been considered in a recent review⁵⁵. None of these forms of administration has been assessed by randomized trials and, as the assessment of radiotherapy remains controversial, the present review will be limited to randomized trials alone.

Preoperative radiotherapy (Table 1)

The rationale of preoperative radiotherapy is that it reduces the viability of tumour cells and so improves local control and survival. It may also facilitate curative resection through tumour downstaging. It has the advantage over postoperative radiotherapy that patients are more likely to complete the course as they are yet to undergo surgery, the tissues are well oxygenated and so more sensitive to radiotherapy, and the majority of the small bowel is excluded from the radiotherapy field by the pelvic contents. Four early trials⁵⁶⁻⁵⁹ used low-dose preoperative radiotherapy of 20 Gy or less and showed no reduction in local recurrence or survival advantage. Later studies have used a higher dose of radiation equivalent to 25 Gy or more, with variable fractionation schedules. Seven of nine such studies⁶⁰⁻⁶⁸ demonstrated a significant reduction in local recurrence compared with surgery alone, five of the studies containing all tumour stages^{62,63,65,67,68} and two containing locally advanced tumours with tethering or fixity^{64,66} only. In terms of 5-year survival, the Manchester study⁶⁴ and the provisional results of the Stockholm II study⁶⁸ both showed a significant improvement in survival with radiotherapy, if survival of patients following curative resection was considered independently. The former study was restricted to locally advanced tumours alone and the only other trial to limit recruitment to this group of patients, Medical Research Council Rectal Cancer Working Party (MRC) II⁶⁶, demonstrated a significant reduction in cause-specific deaths ($P=0.03$) although it failed to reach significance in terms of overall survival ($P=0.09$). The Swedish Rectal Cancer Trial⁶⁷, which randomized over 1100 patients either to preoperative radiotherapy (25 Gy in five fractions over 5 days) followed by immediate surgery or to surgery alone, demonstrated a significant survival improvement with radiotherapy over surgery alone over the whole trial. Local recurrence was reduced significantly for Dukes A, B and C stages. A 10 per cent improvement in survival was demonstrated in patients with Dukes C tumours, which was statistically significant; survival benefit tended towards but failed to reach significance at all stages. The local recurrence rate following surgery alone was comparatively high at 27 per cent. The Swedish Trial⁶⁷, MRC II⁶⁶ and Stockholm II⁶⁸ studies all demonstrated a reduction in the incidence of distant metastases as well as in local recurrence. The mechanism by which a localized therapy can reduce metastases and, in the case of the Swedish trial, result in

Table 1 Randomized controlled trials of preoperative radiotherapy in rectal carcinoma

Group	Year	No. of patients		Regimen		Local recurrence (%)			5-year survival (%)			P for subgroup with curative resection
		Radiation	Control	Dose (Gy)	Frequency	Radiation	Control	P	Radiation	Control	P	
Stearns <i>et al.</i> ⁵⁶	1974	376	414	20	2 weeks	—	—	—	67	65	n.s.	—
VA I ⁵⁷	1975	347	353	20	2 weeks	29	36	n.s.	40	32	n.s.	—
Rider <i>et al.</i> ⁵⁸	1977	60	65	5	1 fraction	—	—	—	39	35	n.s.	—
MRC I ⁵⁹	1984	277	275	5	1 fraction	45	44	n.s.	42	38	n.s.	—
		272	275	20	2 weeks	48	44	n.s.	40	38	n.s.	—
VA II ⁶⁰	1986	180	181	31.5	3.5 weeks	—	—	—	43	46	—	—
Norwegian ⁶¹	1990	155	145	31.5	3.5 weeks	14	21	n.s.	57	58	n.s.	—
EORTC ⁶²	1988	166	175	34.5	3 weeks	15	30	<0.03	52	59	n.s.	0.08
ICRF ⁶³	1994	234	234	15	5 days	17	24	<0.05	—	—	—	—
Manchester ⁶⁴	1994	143	141	20	4 fractions	13	36	0.0001	—	—	—	0.03
Stockholm I ⁶⁵	1995	424	425	25	5 fractions	14	28	<0.01	36	36	n.s.	n.s.
MRC II ⁶⁶ *	1996	139	140	40	4 weeks	32	48	0.04	26	19	0.09	—
Swedish ⁶⁷	1997	583	585	25	5 fractions	11	27	<0.001	58	48	<0.001	—
Stockholm II ⁶⁸ †	1994	272	285	25	5 fractions	10	21	—	—	—	—	<0.05

*Fixed and tethered cancers only, †provisional results only. VA, Veterans Administration; MRC, Medical Research Council; EORTC, European Organization on Research and Treatment of Cancer; ICRF, Imperial Cancer Research Fund, Stockholm, Stockholm Colorectal Cancer Study Group; Swedish, Swedish Rectal Cancer Trial; n.s., not significant

a survival advantage is unknown. One possibility is that lateral lymphatic spread of tumour cells to the pelvic side walls may remain after surgery as a potential focus of local recurrence and a source of distant metastases, and that these cells are destroyed by the radiotherapy. A similar mechanism for adjuvant radiotherapy producing a reduction in local recurrence and distant metastases, and a survival advantage, has recently been proposed for breast carcinoma⁶⁹.

Additional deaths attributable to preoperative radiotherapy occurred in the Stockholm I trial⁶⁵ and the Imperial Cancer Research Fund trial which was run by the Rectal Cancer Group⁶⁷. This took the form of an increase in cardiovascular deaths, particularly in patients aged over 75 years. In the Swedish study⁶⁷ and the Stockholm II trial⁶⁸, there was an increased incidence of wound sepsis in irradiated patients⁶⁵, but the mortality rate was not increased by radiotherapy, although a similar dose and schedule was used in all four trials. This is likely to be explained by a modification of irradiation technique as the latter two trials used three or four beams compared with two in the Stockholm I trial; they also reduced the field to the upper border of the fifth lumbar vertebra rather than the second lumbar vertebra. A dose

equivalent to 25 Gy over 1 week, or 50 Gy over 5 weeks, is considered necessary to kill microscopic collections of cancer cells^{70,71}; such a dose was given in the statistically significant trials of preoperative radiotherapy described here.

Postoperative radiotherapy (Table 2)

The logic of postoperative radiotherapy is that it is possible to select patients at increased risk of local recurrence in the light of knowledge obtained from examination of the resected specimen, such as those with a more advanced stage of tumour. The disadvantages, however, are that the risk of irradiating normal small bowel is increased as this tends to fall down into the pelvis following surgery and that a greater proportion of patients fails to complete the radiotherapy (having just undergone surgery). Only a single randomized trial has compared preoperative and postoperative radiotherapy directly in terms of effectiveness⁷⁹. Comparative radiation doses calculated using the cumulative radiation effect formula were employed and, although survival was identical in both groups, local recurrence was significantly greater in the group undergoing postoperative radiotherapy (13

Table 2 Randomized controlled trials of postoperative radiotherapy in rectal carcinoma

Group	Year	No. of patients		Regimen		Local recurrence (%)			5-year survival (%)		
		Radiation	Control	Dose (Gy)	Time (weeks)	Radiation	Control	P	Radiation	Control	P
Danish ⁷²	1986	244	250	50	2	16	18	n.s.	—	—	—
GITSG ⁷³⁻⁷⁵	1985-1988	50	58	40 to 48	4 5.5	20	24	n.s.	50	43	n.s.
NSABP R-01 ⁷⁶	1988	184	184	46.5	5	16	25	n.s.	41	43	n.s.
Dutch ⁷⁷	1991	88	84	50	5	24	33	n.s.	45	57	n.s.
MRC III ⁷⁸	1996	234	235	40	4	20	34	0.001	41	38	n.s.

GITSG, Gastrointestinal Tumor Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; MRC, Medical Research Council; n.s., not significant

versus 22 per cent, $P=0.02$). The incidence of radiotherapy-related morbidity was negligible in the pre-operative group, with the exception of perineal wound sepsis, but was over 90 per cent in the postoperative group; late complications, such as radiation enteritis, were twice as common with postoperative therapy.

Of the five randomized trials of postoperative radiotherapy⁷²⁻⁷⁸, the first four all reported a reduction in local recurrence which tended towards but failed to reach significance. MRC III⁷⁸ demonstrated a significant reduction in local recurrence but did not show any benefit in survival terms.

Preoperative radiotherapy appears more effective than postoperative radiotherapy, being associated consistently with a reduction in local recurrence when an adequate dose is administered and with a demonstrated survival advantage, particularly after curative surgery. Preoperative staging of rectal carcinoma may be achieved using endo-anal ultrasonography to allow the selection of more advanced tumours for radiotherapy but, although depth of invasion through the bowel wall may be recognized accurately, the assessment of lymphatic spread is less precise⁸⁰.

The use of radiotherapy to allow less radical surgery and avoidance of a permanent colostomy has been considered to a limited extent. Local excision of T₁ and T₂ tumours followed by postoperative radiotherapy has been used by a number of groups with low rates of local recurrence⁸¹⁻⁸³, although local recurrence occurred in 20 per cent of patients with T₃ tumours⁸³. For larger neoplasms, preoperative radiotherapy to downstage the tumour and allow resection followed by coloanal anastomosis increases the proportion of sphincter-saving operations^{84,85}. However, although early survival and recurrence rates are promising, all of these studies were unrandomized and involved small numbers of patients; although they may highlight future areas of useful research, any conclusions from them must be limited.

Chemotherapy

In contrast to radiotherapy, the majority of studies of chemotherapy as adjuvant treatment have focused on colonic rather than rectal carcinoma. Early work on single-agent systemic chemotherapy in colonic cancer failed to provide convincing evidence of benefit, but a meta-analysis by Buyse *et al.*⁸⁶ in 1988 of all randomized studies using 5-fluorouracil (5-FU) as adjuvant therapy up to that time indicated an overall 5-year survival benefit of 3.4 per cent and a reduction in the odds ratio of death of 17 per cent ($P=0.03$). The use of combination chemotherapy provided greater encouragement. Windle *et al.*⁸⁷ reported a benefit from postoperative adjuvant 5-FU and levamisole, and a further study of similar therapy in resectable stage II and III colonic cancer reported a significant improvement in 5-year disease-free survival in patients with stage III tumours⁸⁸. In 1990 the American Intergroup Study⁸⁹ reported a reduction in overall mortality rate of one-third in patients with Dukes C tumours with the administration after surgery of a 1-year course of 5-FU and levamisole, although levamisole alone was of no benefit. These results were maintained in the final report at a median follow-up of 6.5 years⁹⁰, with a reduction in tumour recurrence of 41 per cent. Studies of 5-FU combined with high-dose folinic acid for 6 months after operation have demonstrated a significant improvement in survival in patients with Dukes C colonic

cancer⁹¹⁻⁹³. Provisional results from ongoing trials indicate that there is no increased benefit from 12 months of therapy compared with the benefit obtained by 6 months of treatment⁹⁴, that there is no significant therapeutic difference between the addition of levamisole or of folinic acid to 5-FU⁹⁵, and that the addition of levamisole to 5-FU and folinic acid provides no advantage⁹⁶. An ongoing Dutch trial⁹⁷, however, has shown no benefit from 5-FU plus levamisole compared with no treatment. Overall, 5-FU-containing adjuvant chemotherapy appears to generate a survival benefit in patients with Dukes C colonic carcinoma, although this has not been demonstrated universally. The optimum combination remains uncertain and the outcome of further studies is awaited.

Most work on chemotherapy has involved colonic tumours rather than rectal carcinoma alone. Evidence of a beneficial effect of adjuvant chemotherapy for rectal carcinoma has been derived partially from the studies of chemotherapy in colonic carcinoma, as no difference has been shown between rectal and colonic carcinoma in the response of the tumour to palliative chemotherapy. The only randomized trials to assess postoperative chemotherapy specifically on rectal carcinoma are the Gastrointestinal Tumor Study Group (GITSG) trial⁷³⁻⁷⁵ and the National Surgical Adjuvant Breast and Bowel Project (NSABP)⁷⁶. Radiotherapy was involved in both, but in the surgery plus chemotherapy (methyl chloromethylcyclohexylnitrosourea (MeCCNU) plus 5-FU for 18 months) arm of the GITSG trial, there was no significant improvement in survival from the addition of chemotherapy. The NSABP trial reported a significant improvement in disease-free survival with the addition of chemotherapy (MeCCNU, vincristine, 5-FU) and in overall survival in a subgroup of men aged under 65 years. A Swedish study⁹⁸ of chemotherapy (MeCCNU, vincristine, 5-FU) in colorectal cancer assessed the effect on patients with rectal carcinoma as a subgroup, but found no survival benefit.

Regional chemotherapy has been investigated in the form of postoperative liver perfusion with 5-FU (as opposed to systemic administration) as the liver is the commonest site of distant spread of colorectal tumours. Taylor *et al.*⁹⁹ randomized 244 patients after resection of colorectal carcinoma at all stages to postoperative portal vein infusion of 5-FU and heparin or no additional treatment. They demonstrated a reduction in liver metastases and a significant survival advantage in patients with Dukes C rectal tumours. The Swiss Group for Clinical Cancer Research¹⁰⁰ demonstrated a 21 per cent reduction in risk of disease recurrence using portal vein infusion of 5-FU, mitomycin C and heparin as adjuvant therapy, randomizing 469 patients following surgery for colonic or rectal tumours. A similar trial by the North Central Cancer Treatment Group (NCCTG)¹⁰¹, however, randomizing 224 patients and using portal vein infusion of 5-FU and heparin, showed no difference in liver metastases or 5-year survival rate between the two groups. A meta-analysis of ten published trials of portal vein infusion¹⁰² indicated a 20 per cent reduction in risk of death from colorectal cancer with a significantly greater benefit in patients with Dukes C carcinoma compared with Dukes B carcinoma. The survival benefit from portal vein infusion of 5-FU is similar to that of systemic chemotherapy in patients with Dukes C tumours. Hepatic artery infusion of chemotherapy has been used to treat established liver metastases with some benefit^{103,104} but its role

as adjuvant therapy is uncertain. The Adjuvant X-ray and 5-FU Infusion Study (AXIS) trial¹⁰⁵ is likely to provide further information about the benefit of intraportal chemotherapy and will give additional information on the role of radiotherapy.

Chemoradiotherapy

Five trials of radiotherapy combined with chemotherapy as adjuvant treatment for rectal carcinoma have been published^{73-75, 106-109} (Table 3), although preliminary results only are available from the most recent two. The first was the European Organization on Research and Treatment of Cancer (EORTC) trial¹⁰⁶ which compared preoperative radiotherapy with preoperative radiotherapy and 5-FU. There was no difference in local recurrence or survival between the groups and the radiotherapy technique used resulted in severe toxicity. One limb of the GITSG trial⁷³⁻⁷⁵ considered postoperative radiotherapy with 5-FU, followed by 18 months of systemic chemotherapy (MeCCNU and 5-FU). While this produced a significant reduction in local recurrence and an improvement in overall survival when the results were adjusted for main prognostic factors, the number of patients involved was small. Another American trial, NCCTG¹⁰⁷, compared postoperative radiotherapy (45–50 Gy) with postoperative radiotherapy plus 5-FU, which was preceded and followed by a cycle of systemic chemotherapy with 5-FU plus MeCCNU; 204 patients were randomized and the combined chemoradiotherapy produced a significant reduction in local recurrence and improvement in overall 5-year survival. The two remaining trials, the NSABP R-02¹⁰⁸ and the Norwegian¹⁰⁹ trial, both assessed postoperative radiotherapy and 5-FU, respectively against surgery followed by chemotherapy and against surgery alone. Both have yet to complete a 5-year follow-up but early results suggest a significant reduction in local recurrence, from 11.3 to 6.7 per cent in the NSABP R-02 trial and from 30 to 12 per cent in the Norwegian trial. The Norwegian trial has also shown an early survival benefit; however, the local recurrence rate in the surgery

alone group was substantial and a reduction in local recurrence from this level could account for such a result.

The National Institutes of Health Consensus Conference in the USA in 1990¹¹⁰ concluded that combined postoperative chemotherapy and radiotherapy should be given as adjuvant therapy to all patients with stage II and III rectal carcinoma. The recommended treatment was 45–55 Gy after surgery with 5-FU and MeCCNU chemotherapy. Radiotherapy was considered to be important to reduce local recurrence of disease, although its contribution to survival benefit was uncertain; systemic chemotherapy was recommended for improvement in survival. Since that time, MeCCNU has been recognized as having no role in adjuvant therapy^{111,112} and survival has been shown to be improved with the protracted venous infusion of 5-FU during postoperative radiotherapy (compared with bolus injections)¹¹². Chemotherapy may potentiate radiotherapy by increasing the radiosensitivity of the tumour, but the biological basis of combination therapy remains uncertain. The toxicity of combined adjuvant therapy is considerable and can substantially reduce compliance⁶¹. Furthermore, chemoradiotherapy has been shown to have a major detrimental effect on bowel function in the long term¹¹³.

Evidence of the potential benefit of preoperative radiotherapy over postoperative radiotherapy has raised interest in the administration of preoperative chemoradiotherapy. Rich *et al.*¹¹⁴ have investigated the use of protracted preoperative infusion of 5-FU combined with preoperative radiotherapy (45 Gy) in 77 patients with T₃ rectal cancer. Early results show an increase in sphincter-saving procedures, and an overall survival rate of 83 per cent at a median of 27 months after surgery. Current multicentre trials, in both the USA and Europe, are recruiting patients to assess preoperative chemoradiotherapy. The NSABP R-03 trial in the USA¹¹⁵ is comparing one course of preoperative chemotherapy followed by combined chemotherapy and radiotherapy, surgery and then postoperative chemotherapy to the standard American treatment of surgery followed by postoperative chemotherapy, radiotherapy with concurrent chemotherapy, and then further chemotherapy. Early

Table 3 Randomized trials of combined radiotherapy and chemotherapy in rectal carcinoma

Group	Year	Therapy	No. of patients	Local recurrence		5-year survival	
				Rate (%)	P	Rate (%)	P
EORTC 4074 ¹⁰⁶	1984	RT _{preop} + 5-FU	126	15	n.s.	46	n.s.
GITSG ⁷³⁻⁷⁵	1985	RT _{preop}	121	15		59	
		RT _{postop}	50	20	n.s.	52	n.s.
		MeCCNU + 5-FU	48	27	n.s.	56	
		RT _{postop} /5-FU, MeCCNU + 5-FU	46	11	0.009	59	
		Surgery alone	58	24	—	46	
NCCTG ¹⁰⁷	1991	RT _{postop} /5-FU, MeCCNU + 5-FU	104	13	0.036	57	0.02
		RT _{postop}	100	25		47	
NSABP R-02 ¹⁰⁸	1994	MOF	741	11		—	
		5-FU/Fol					
		RT _{postop} + MOF			0.045		
Norwegian ¹⁰⁹	1995	RT _{postop} + 5-FU/Fol		7			
		RT _{postop} + 5-FU	72	12	0.01	69	0.05
		Surgery alone	72	30		49	

EORTC, European Organization on Research and Treatment of Cancer; GITSG, Gastrointestinal Tumor Study Group; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; RT_{preop}, preoperative radiotherapy; RT_{postop}, postoperative radiotherapy; 5-FU, 5-fluorouracil; MeCCNU, methyl chloromethylcyclohexylnitrosourea; MOF, semustine, vincristine and 5-FU; Fol, folic acid; n.s., not significant

results demonstrate similar patient tolerance between the two treatments and a trend toward increased sphincter preservation in the preoperative arm, but it is too early for effects on recurrence and survival to be known. In Europe, the EORTC Rectal Cancer Trial 22921¹¹⁶ is randomizing patients with T₃ and T₄ tumours, comparing preoperative radiotherapy with preoperative radiotherapy plus preoperative chemotherapy (5-FU and folinic acid), with or without postoperative adjuvant chemotherapy.

Immunotherapy and other modalities

The theory of modulating the immune system to combat tumour cells has generated substantial interest, although results so far have been limited. Levamisole was considered to have an immunostimulatory effect but it has not been shown to be beneficial when used in isolation^{89,117}. Non-specific immunotherapy using *Bacillus Calmette-Guérin* (BCG)¹¹⁸, interferon¹¹⁹ or polyadenylicpolyuridylic acid¹²⁰ has failed to show any additional benefit in the treatment of colorectal cancer. Specific immunotherapy using autologous tumour cells plus BCG vaccine has demonstrated a benefit in disease-free and overall survival¹²¹. The number of patients involved in the study was small, however, and the benefit was evident only in subgroup analysis; it was detected in patients with colonic tumours but not in those with rectal tumours. A similar trial involving a greater number of patients is ongoing in Holland¹²².

The concept of using tumour-directed monoclonal antibody as an agent that could be targeted specifically at the tumour is attractive. While early studies showed no benefit, Riethmuller *et al.*¹²³ recently reported a significant improvement in survival in a randomized trial using 17-1A monoclonal antibody as adjuvant therapy in patients with Dukes C colorectal carcinoma after complete resection of the tumour. After a median follow-up of 5 years, antibody therapy reduced the overall death rate by 30 per cent and decreased the recurrence rate by 27 per cent, accompanied by a low toxicity rate. The therapy appeared to reduce distant metastases while having no effect on local recurrence, and the survival benefit is similar in magnitude to that shown by 5-FU-containing chemotherapy in patients with colonic cancer or chemoradiotherapy in those with rectal cancer. The trial randomized 180 patients and a current multicentre trial is investigating the potential of 17-1A monoclonal antibody as an adjuvant therapy in combination with 5-FU.

Intraoperative photodynamic therapy combined with a systemic photosensitizer has shown promising results in animal studies¹²⁴ and appears to have a low toxicity when applied to humans¹²⁵. Studies on its clinical application are awaited.

Conclusions

Extensive research has identified and refined a variety of treatment modalities for the management of colorectal carcinoma but the question of the optimum combination for a particular patient remains unanswered. Further investigation of the mechanisms of local and distant tumour spread and recurrence, and of the action of various treatment modalities, are needed for the consideration of complementary therapies. In the case of rectal carcinoma, total mesorectal excision reduces the local recurrence rate, logically because it leaves fewer

tumour cells in the pelvis. It has been adopted as the standard surgical procedure in the UK¹²⁶ but one must question whether it is adequate alone to remove the lateral spread of isolated tumour cells and whether all surgeons can produce results as good as those of Heald *et al.*³². Even with 'curative' surgery the overall mortality rate from rectal carcinoma remains substantial. Radiotherapy, however, destroys microscopic tumour deposits in the pelvis and has been shown to reduce local recurrence of rectal cancer. If there is known residual tumour in the pelvis it is understandable that radiotherapy would reduce local recurrence, but most of the trials that have shown a benefit have involved preoperative radiotherapy and complete surgical resection. It is possible that the diagnosis of a curative resection would be revised if the lateral margins were examined more closely (as has been highlighted in histological studies²⁸) but this is unlikely to account for all of the reduction in local recurrence generated by radiotherapy. Until recently, no trial of radiotherapy and surgery had demonstrated a survival advantage over surgery alone, but the Swedish Rectal Cancer Trial⁶⁷ has now demonstrated such a survival benefit in a well constructed randomized study involving a substantial number of patients. It remains uncertain whether a short course of high-dose preoperative radiotherapy is complementary to total mesorectal excision or compensatory for inadequate surgery; this could be determined only by a further clinical trial. As the morbidity of this form of radiotherapy appears low, it seems reasonable to administer it to all patients with rectal tumours where the suspicion of nodal spread is high. As radiotherapy has shown a survival benefit, is it affecting the systemic spread of tumour cells from the pelvis? Both systemic and portal chemotherapy have shown a survival benefit in patients with Dukes C tumours, in whom it is assumed that the systemic spread of tumour cells is increased, but the evidence is more convincing for colonic tumours.

Present guidelines for the management of resectable colorectal carcinoma differ from country to country. The current American consensus¹¹⁰ for rectal carcinoma is for surgical resection followed by adjuvant chemoradiotherapy for all tumours that extend through the muscle of the bowel wall or have nodal spread (tumour node metastasis stages II and III or Dukes stages B and C). For colonic carcinoma, the addition of postoperative systemic chemotherapy with 5-FU and levamisole for stage II or Dukes C tumours is recommended. The view on this side of the Atlantic is more selective. The recommendations of the Royal College of Surgeons of England and the Association of Coloproctology¹²⁶ are similar for colonic carcinoma, but for rectal carcinoma they favour total mesorectal excision, preoperative high-dose radiotherapy when the surgeon is not confident of achieving a curative resection, postoperative 5-FU-containing chemotherapy for Dukes C tumours, and postoperative radiotherapy for patients with involved circumferential margins. Optimum surgical excision, radiotherapy to manage tumour cells that are not resected and chemotherapy for disseminated tumour cells is logical, but to move from guidelines to interventions for individual patients requires methods of selecting those at increased risk of recurrence. Currently, the frequency of administration of chemotherapy to patients with Dukes C colorectal carcinoma in the UK is low¹²⁷ and further evidence of survival benefit outweighing side-effects would encourage usage. Identification of additional prognostic factors would be useful in the risk-

benefit assessment made when considering additional adjuvant therapy. Improvements in preoperative staging methods for rectal tumours may detect lymphatic spread and identify those for whom surgery alone is likely to be inadequate and for whom additional radiotherapy is appropriate. In parallel with refining the implementation of current treatment modalities for individual patients, research into alternative forms of adjuvant therapy (such as immunotherapy) should prove worthwhile. The results of current trials such as QUASAR (Quick and Simple and Reliable) and AXIS may also determine more effective systemic therapies for colonic and rectal carcinoma.

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Review

Endoprotheses for colonic strictures

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Background Patients who present with large bowel obstruction often undergo emergency surgical intervention with its attendant risk of morbidity and death. A colostomy may be inevitable and this detracts from the patient's quality of life, especially when palliation is the only option.

Methods This review examines the possibility of a more conservative approach using metallic stents to relieve colonic obstruction, either as the first stage of a curative surgical procedure or for palliation without surgery. The various stents available are examined.

Results Case reports show that relief of obstruction can be achieved in over 80 per cent of patients, allowing subsequent elective surgery or achieving palliation for several months. Complications are rare but include colonic perforation, particularly when predilatation of the stricture has to be performed. Such complications are generally recognized early and patients can proceed to surgery and colostomy, as would previously have been conventional treatment; on occasion a small leak may be treated conservatively with success. The advent of newer endoprotheses which do not require active dilatation may improve the rate of successful deployment and lessen the risk of perforation.

Conclusion The development of new endoprotheses has allowed their adaptation for use in the colon and, perhaps, the distal small bowel. The technology is evolving rapidly and warrants serious consideration in selected patients with large bowel obstruction before embarking on surgery. There is an urgent need for a controlled trial to establish whether such intervention for malignant strictures, potentially curable by surgery, leads to an increased risk of metastatic disease.

The use of stents to treat strictures in most parts of the body has found increasing favour in recent years. The results in vascular pathology are exciting; stents have found application in coronary artery disease after angioplasty¹, major vessel disease (both occlusive and aneurysmal)^{2,3} and treatment of portal hypertension using transjugular intrahepatic portacaval shunts⁴. Certain urethral strictures have proved suitable for stenting⁵ and increasing use of these appliances is reported for the treatment of tracheal and bronchial strictures, both after surgery and neoplastic⁶. Improvements in structural design and more sophisticated delivery systems have allowed placement of flexible self-expanding stents using minimally invasive techniques. The procedures are well tolerated and have proved equal or superior to conventional surgery in many instances, especially in palliative circumstances.

Application of stents in the gastrointestinal tract

In the gastrointestinal tract, stents have been particularly successful in the palliation of oesophageal and choledochal strictures^{7–9}, but they have been little used elsewhere in the gut. At first sight this is surprising, as there is clearly a need to deal with strictures affecting the colon and, less commonly, the small bowel (particularly the duodenum in advanced pancreatic malignancy). The explanation may be that experiences with older technology involving relatively rigid tubes proved unsatisfactory, especially in the colon. The first tubes were designed for

oesophageal use and were stiff, difficult to insert and required preliminary dilatation with its associated risk of morbidity and death. They were prone to bolus obstruction and migration, and were essentially a short-term measure. The same considerations apply to plastic biliary endoprotheses, which work well for a few weeks or months but then need replacement. In the lower gut, where wall motility for luminal transit is a major factor, rigid tubes of any significant length run the risk of obstruction either by bolus impaction or inhibition of peristalsis. In addition, dilatation of colonic strictures is technically difficult, partly because of limited access but mainly because of the high mortality rate associated with even a small perforation or split.

In the colon, therefore, patients with an inoperable stricture have had little choice but to undergo surgery, either in the form of a colocolonic bypass or, more usually, palliative colostomy. Perhaps of more importance is the patient who has an operable stricture but presents with an acute obstruction, thereby precipitating urgent surgical intervention with its concomitant risk of complications and death. On occasion, it is possible temporarily to deflate an obstructed colon using a large-bore nasogastric or thoracotomy tube¹⁰, but this rarely works well unless flatus is the main problem. The tube blocks readily, given it is usually only wide enough to cross a stricture of critical diameter, often of the order of 1 cm. Nevertheless, when the procedure works it converts an emergency into an elective procedure and, if bowel cleansing can be achieved, a primary resection can then be performed on a resuscitated and properly prepared patient. If it does not work, surgical intervention may be delayed and clearly this is of no benefit.

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Stent technology

Fortunately, the situation is changing and it is proving possible to adapt the new technology to the lower gut. One is no longer limited to rigid, tubular stents following the development of the self-expanding metal varieties devised by Gianturco in 1985 for endovascular use¹¹. The early stents were crude structures of varying configuration with wide interstices. Rapid improvements have taken place allowing more complex shapes with a tighter mesh, and more compact and sophisticated delivery systems. These stents have the advantage of remarkable flexibility and can tolerate a greater degree of curvature than rigid tubes.

There are basically two types of metallic systems, expandable and self-expanding. The expandable version, such as the Strecker stent¹², must be positioned inside a predilated stricture and then balloon dilated on to the wall where it takes up its preconfigured shape. A problem is that such stents may not conform properly or may subsequently collapse or migrate. They may also be difficult to remove subsequently should this prove necessary.

The self-expanding Gianturco and Wallstent (Schneider, Bülach, Switzerland) types derive their expansile force as a result of their geometric structure; they spring into shape on release. Unfortunately, unless the diameter is perfectly gauged, the stent may require further dilatation by balloon to avoid migration, if too narrow, or, if too wide, may cause undesirable erosion and even perforation. These stents may have hooks in the external wall or have sharp pointed wire ends for additional fixation, further increasing the risk of erosion or perforation. In addition, the mesh interstices are often relatively large allowing tissue ingrowth and this may be undesirable. The latest stents are made of nitinol, an alloy of nickel and titanium developed originally for use in the aerospace industry¹³. This has the remarkable property of 'shape memory' and reverts to a predetermined configuration after release from distortion in the delivery system. The key benefit is that such a stent applies a large radial force spontaneously and evenly and, better still, only achieves its final diameter after 2–5 days, thus helping to provide optimal yet gentle dilatation of the stricture. This property often means that preliminary dilatation of the stricture is not necessary other than to permit passage of the insertion system. Dislodgement and stent migration are also less of a problem, avoiding the need for sharp hooks in the stent structure. An additional property is that nitinol stents retain extraordinary flexibility because of the fineness of their mesh. This permits some peristaltic movement, which can be observed at endoscopy.

The use of such stents in the oesophagus has proved highly successful, with a low mortality and morbidity rate, because they are easier to insert and deploy than conventional tubes. Indeed stents lined with a material coating such as Dacron (Du Pont, Stevenage, UK) or plastic have proved successful in the treatment of tracheo-oesophageal fistula¹⁴; such stents are designed to prevent ingrowth of tumour or granulation tissue through the interstices of the mesh. Unfortunately, such a coating makes the stent more likely to migrate as it is on the outside of the device, reducing friction with body tissue. It may be that new designs with the lining on the inside will solve the problem, but such stents have yet to be made available. Tumour ingrowth is not often a problem given

the lifespan of most patients undergoing palliation, but if it does cause difficulty after 3–6 months it may be possible to destroy the ingrowth endoscopically using an argon beam diathermy technique. This method is recommended by the stent manufacturers in preference to laser or photodynamic therapy, both of which may disrupt the prosthesis, although they have both been used successfully¹⁵. There is also the additional, if more expensive, option of inserting a second stent inside the first, either to create a longer tube or to induce pressure necrosis of any tumour ingrowth.

Literature review

A search of the recent English literature provides only a few reports of stenting procedures in the colon but the numbers are increasing gradually. The first reported use of a metal stent was by Dohmoto in 1991¹⁶ followed by Itabashi *et al.*¹⁷ and Cwikiel and Andren-Sandberg¹⁸ in 1993. These early reports were based on one or two patients receiving palliative treatment, but in 1994 Tejero *et al.*¹⁹ reported two patients who were stented to allow disimpaction before undergoing definitive surgery a few days later. A larger series of 15 cases from Saida *et al.*²⁰ describes an experience of short-term preoperative stenting.

Other small series have followed, with recent reports of 13 cases from Canon *et al.*²¹, an update from Tejero *et al.*²² who achieved relief of acute obstruction in 35 of 38 cases, and nine patients with a variety of intestinal strictures from Kozarek *et al.*²³. A variety of stents have been used but the trend is clearly towards the more flexible, closer knitted and self-expanding nitinol prostheses, such as the Ultraflex (Boston Scientific Corporation, St Albans, UK) originally designed for oesophageal use. Grund²⁴ used 19 such stents in 16 patients with primary, recurrent or extrinsic malignant compression of the distal sigmoid colon or rectum, with strictures of between 3 and 12 cm long. A success rate of 80 per cent at 42 weeks' follow-up was achieved.

Complications have generally been few and straightforward, consisting mainly of either failure to deploy the stent across the stricture or of subsequent migration. However, there are several reports of colon perforation, nearly all caused during an attempt to dilate the stricture either to allow passage of the delivery system or to fix the stent on to the bowel wall. Affected patients tended to have more severe strictures; most required surgery and a defunctioning colostomy, although some without symptoms and who were diagnosed only by free gas on radiography were successfully treated conservatively.

There exists a single report²⁵ of a benign postanastomotic stricture treated with a Wallstent prosthesis with a superb outcome at 1 year. Complete epithelialization of the prosthesis had taken place.

There seems to be no reason why stents cannot be used to deal with colovesical and colovaginal fistulas. One of the early case reports¹⁸ described such a case which succeeded without a coated stent, avoiding the increased risk of stent migration.

Clinical experience

The author's limited experience of six cases to date has confirmed the value of the procedure in advanced malignancy, involving strictures of between 7 and 12 cm

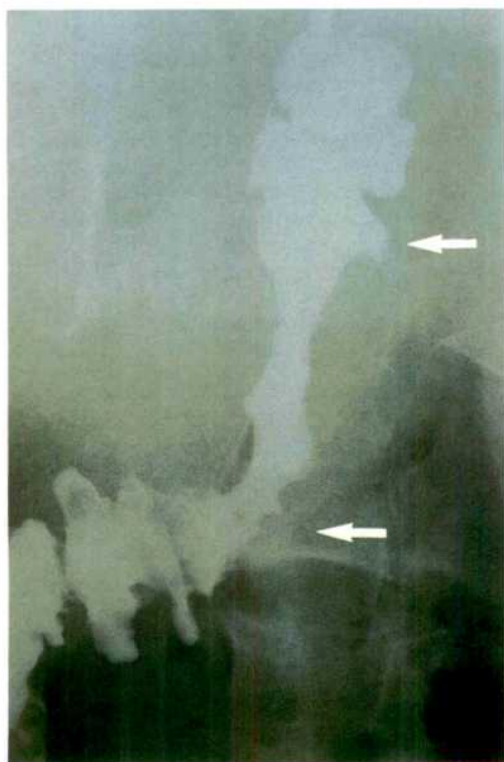


Fig. 1 Contrast enema showing long rectosigmoid stricture (approximately 12 cm)

long and as high as 40 cm from the anal verge. A combined colonoscopic and radiological procedure was used to insert nitinol stents of between 7 and 15 cm length and up to 22 mm expanded diameter (Ultraflex). So long as a paediatric colonoscope was able to pass the bulk of the stricture, stenting was possible without preliminary dilatation even if it had to be done in two stages using overlapping prostheses as the stricture opened up. The first case attempted was that of a 72-year-old lady with an inoperable rectosigmoid carcinoma at the left pelvic brim, involving the left ureter and with liver and lung metastases. The ureter was also stented; the patient remains well and symptom free over 10 months later. She has undergone repeat colonoscopy at intervals of 3 months and minor tumour ingrowth has been ablated using an argon beam coagulation device (Erbe, Tübingen, Germany).

Figs 1 and 2 show a second example, a 43-year-old man with an inoperable rectosigmoid carcinoma 12 cm in length which was successfully stented using a 15-cm prosthesis. The flexibility of the stent is well demonstrated as is the remarkable preservation of the lumen. This patient remains well palliated 7 months later.

Another patient with a sigmoid stricture secondary to longstanding Crohn's colitis has also been stented successfully and this is the first report of such a case. The patient is an 84-year-old man with endstage respiratory failure and a severe kyphosis who refused colostomy. A limited follow-up of only 12 weeks has been uneventful.

Discussion

In the colon, modern stents are attractive as they are flexible, allow some wall movement and conform to bends



Fig. 2 Fully deployed stent (15 cm)

in the bowel with remarkable ease. Insertion may be performed either by a radiologist or an endoscopist and, provided it is possible to introduce a guidewire across the stricture and enough dilatation can be achieved to pass a 15-Fr gauge delivery device, the system may be deployed under fluoroscopic control to achieve maximum dilatation over the next few days. In this way the risk of perforation is minimized. A long stricture may be bridged by inserting sequential stents with little or no loss of flexibility. If a stent of non-memory material is used, maximum dilatation should be attempted at insertion, using an angioplasty balloon as required. This may need to be repeated after a few days, but this is a technique which seems to increase the risk of perforation.

The entire procedure can usually be carried out on an outpatient basis with minimal sedation and requires only simple preparation. Following successful insertion, the patient is given instruction about diet and the maintenance of soft bowel motions, although this may not be strictly necessary once the obstruction is cleared. The patient may then proceed to planned surgery or adjunctive palliative treatment as appropriate.

In theory, strictures at any point in the colon may be stented but, until very recently, the delivery systems available were designed primarily for oesophageal insertion with a length of about 65 cm, limiting access to the distal left colon. It is possible to achieve more proximal access by 'shortening' the colon with a colonoscope. A new stent system is now available which passes through a 3.6-mm channel for deployment through the scope. This endoprosthesis (Wallstent Enteral; Schneider) is only 10 Fr in diameter and does not need predilatation or postdeployment anchoring, yet opens up

to 22 mm diameter and up to 90 mm in length. It has been successfully deployed on the ascending colon (P. Fairclough, personal communication). In the proximal gut, the duodenum is certainly accessible and Howell *et al.*²⁶ have reported eight patients with advanced pancreatic cancer in whom the duodenum was stented with a biliary Wallstent giving fair results. These stents can be bettered by the larger diameter devices now available. Palliation of recurrent tumour after gastric surgery has also been reported²⁷.

Cost effectiveness

A major criticism of the technique has been the cost. Stents are expensive at between £800 and £1000 each, and to this must be added the cost of radiology and ancillary services. However, they are inserted under sedation and, in planned cases, as an outpatient procedure. When compared with the cost of surgery for bypass or colostomy the stent option seems reasonable. If one adds the benefit of quality of life for the patient, it is money well spent.

The future

There is a need to collect more information on the use of self-expanding stents in the bowel in order to develop systems designed specifically for this area rather than make do with those adapted from oesophageal use. The new Wallstent enteral endoprosthesis is a welcome start and raises the option of access to the small bowel, either via an enteroscope or via a laparoscopically assisted approach. The memory effect of nitinol allows more adventurous and complex shapes to be made so that a wider inlet and outlet can form at either edge of the stricture. It may also be an advantage to try to achieve a slightly larger diameter than the 18–20 mm now available, although any benefit from this remains to be demonstrated. Stents which are readily extractable or biodegradable may be useful for short-term use, particularly in benign conditions. This raises the question of the role such materials may have in the treatment of inflammatory strictures, especially in Crohn's disease. It is not known if the presence of a stent predisposes to abscess or fistula formation; perhaps it might actually prevent it.

Stents with coatings designed to prevent tumour ingrowth need to be developed either by impregnation of the coat with a pharmacologically active agent²⁸ or by using radioactive wire. Indeed stents capable of beta particle emission are being evaluated as a means of preventing atheromatous recurrence²⁹ and the temptation to use these, or other emitters, for local control of advanced malignancy will be irresistible.

Finally, while there are few criticisms of the efficacy of colonic stenting for palliation of advanced malignancy, there are serious concerns about its use in primary tumours, where manipulation of a potentially localized and curable carcinoma may predispose to metastatic disease. This question remains unanswered and, more worryingly, unaddressed. There is an urgent need to establish a protocol for a clinical trial to quantify the risks before the technique is applied to all cases of acute obstruction. Until then selection of suitable patients must be made with considerable caution.

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An 8-year experience of hepatic resection: indications and outcome

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Background Most reports highlighting decreasing operative morbidity and mortality rates following hepatic resection have focused on the management of metastatic disease. Information on the full range of hepatic disease is lacking.

Methods The indications for hepatic resection in a specialist hepatobiliary unit have been reviewed and the operative morbidity and mortality rates assessed.

Results Among 129 patients undergoing 133 hepatic resections between October 1988 and September 1996, the principal indication for resection was hepatic malignancy (102 resections), metastatic in 66 cases. Other indications included contiguous tumour ($n = 20$), primary tumour ($n = 16$) and benign disease ($n = 31$). Some 116 procedures were classical anatomical resections. Blood transfusion was required in 40 per cent of cases but major morbidity occurred in 20 per cent. There were six deaths following surgery, five of which were due to hepatic failure and followed resection for malignancy or trauma. The 3-year survival rate in patients resected for colorectal metastases was 65 per cent.

Conclusion This experience has demonstrated an increasing role for hepatic resection in a wide variety of hepatobiliary pathologies. Despite the low postoperative mortality rate, the significant risk of complications in the postoperative period serves to emphasize the need for careful selection of patients for such surgery, which should be undertaken in specialist centres.

Numerous recent reports attest to decreasing operative morbidity and mortality rates following hepatic resection. Mortality rates of approximately 5 per cent appear to be maintained even in elderly patients^{1–4} and for patients with malignant disease⁵ although mortality is increased for cirrhotic patients. Refinements in operative technique, better selection of surgical candidates, an increasing trend for the resection of hepatic metastases and advances in perioperative care are all thought to be responsible for reducing postoperative risk. Technical improvements have contributed to the prevention of operative blood loss, which, in conjunction with the extent of resection, appears to correlate with operative morbidity^{1,5–7}.

Most reports of liver resection have come from the continent of Europe and from the USA, whereas the reported experience from the UK has been limited largely to descriptions of technique with only a few reports including survival and morbidity data^{8–11}. An 8-year experience of hepatic resection performed in the specialist hepatobiliary unit at the authors' institution was reviewed to document the indications and types of resection, and to determine the causes of operative morbidity and mortality.

Patients and methods

All patients reviewed underwent hepatic resection between October 1988 and September 1996. Preoperative evaluation varied according to the disease process but included computed tomography (CT) in all patients, CT angiography in patients with metastatic disease, and angiography in those with cholangiocarcinoma and primary hepatic malignancy. In addition, over the last 4 years laparoscopic ultrasonography was carried out in patients with suspected hepatic malignancy. All patients with malignancy were assessed to exclude the presence

of extrahepatic dissemination of tumour and, in patients with hepatic metastases, to exclude primary recurrence of tumour.

Operative technique

Broad-spectrum antibiotics (cefotaxim 1.5 g; Roussel Laboratories, Uxbridge, UK) were given intravenously at induction of anaesthesia. Subcutaneous heparin 5000 units was given twice daily over the operative period as prophylaxis against deep vein thrombosis. Central venous pressure was monitored continuously during operation and maintained below 5 mmHg to minimize hepatic venous congestion and to reduce blood loss.

Exposure was obtained by means of a bilateral subcostal incision, and the costal margins were retracted upward using Doyle's blades. Further mechanical retraction was by means of an Omni-tract device (Minnesota Scientific, Saint Paul, Minnesota, USA). Intraoperative ultrasonography (Aloka SSD 500; Keymed, Southend-on-Sea, UK) was used to assess the lesion and define its precise position with respect to the portal pedicles and hepatic veins. In patients with suspected neoplasia, ultrasonography was used to exclude the presence of further lesions in the residual liver.

The resection techniques used were based on those described by Garden and Bismuth¹² and were designed to minimize blood loss and provide demarcation of the segments to be resected by means of early vascular control of the portal venous and arterial inflow. Intrahepatic ligation of appropriate hepatic veins and portal branches was used to prevent further blood loss and inadvertent injury to abnormally positioned vessels and ducts. The liver was mobilized by division of the peritoneal attachments and exposure of the extrahepatic portions of the appropriate hepatic veins and of the retrohepatic vena cava by division of venous branches between ties or Absolok clips (Ethicon, Edinburgh, UK). For left lobectomy (segments II and III) or extended right hepatectomy including segments IV and VIII, the falciform ligament was used as a guide to the individual ligation of the extrahepatic segmental pedicles. Transection of the liver was by means of a Cavitron Ultrasonic Surgical Aspirator (CUSA System 200 Macro-Dissector, Model 200M; Cavitron Surgical Systems, Stamford, Connecticut, USA). Haemostasis was achieved using argon beam coagulation (Force GSU System; Valleylab, Boulder, Colorado, USA) for small vessels and suture or clip ligation of larger vessels or bile duct branches.

Up to two tube drains (28 Fr) were left in place for the detection of bleeding or bile leakage. Patients were nursed in a surgical high-dependency unit with continuous monitoring of central venous and arterial blood pressure, hourly urine volumes were recorded after operation for 24 h. Monitoring of hepatic function included measurement of blood glucose and serum lactate levels, and prothrombin time, on an individualized basis according to the extent of resection and preoperative liver function.

Data collection

At the time of discharge from hospital, patient details were entered on a database which included demographic data, date of operation and hospital discharge, operative blood loss and number of units of blood transfused, and complications. Complications or deaths occurring either within 30 days or before hospital discharge were considered as perioperative. Complications were considered to be minor if discharge was not delayed and as major if discharge was delayed or further intervention was required. Further information regarding complications, deaths and tumour recurrence was added to the database at the time of 6-week, 6-month and annual outpatient follow-up and through communication with the general practitioner.

Results

Between October 1988 and September 1996, 133 hepatic resections were undertaken in 59 women and 70 men. The median age of patients undergoing resection was 59 (range 21–80) years. Three patients underwent multiple resections at initial presentation and four had further resection for recurrent disease. The indications for resection were benign disease in 31 patients, including seven for symptomatic hepatic cysts and six for focal nodular hyperplasia (*Table 1*). Among the 102 resections for malignant disease, there were 16 primary tumours. Colorectal metastases (58 resections) were the principal indication for resection in the group with secondary malignancy, and cholangiocarcinoma (16 cases) was the main indication for resection of contiguous tumour (*Table 1*). The 116 classical hepatic resections included hepatectomy in 72 cases, extended hepatectomy in 28 and left lobectomy in 16 (*Table 2*). The remaining 17 cases included resections of one to three segments (15 cases) or consisted of non-anatomical wedge resections (two cases) (*Table 2*). The median anaesthetic time was 300 (range 95–630) min.

The transfusion requirement for the various hepatic resections is listed in *Table 3*. Blood transfusion was required in only 53 resections (40 per cent). Transfusion requirement was similar for resections of benign or malignant disease but there were two cases of massive transfusion. One patient underwent right hepatectomy for major hepatic trauma with hepatic vein involvement and required 74 units of blood during operation. This was the only patient in whom thoracotomy was undertaken to improve exposure of the liver. The other patient received 32 units of blood during extended right hepatectomy for carcinoid syndrome with hepatic venous congestion secondary to right heart failure. The former patient is alive and asymptomatic at 6 years but the second patient died at 4 years from disseminated carcinoid metastases.

Early complications

The median postoperative hospital stay in surviving patients was 11 (range 5–83) days. Minor perioperative

morbidity occurred in 25 per cent of patients and included atelectasis or chest infection responding to physiotherapy and antibiotics (17 patients), reactive right pleural effusions (four), urinary tract infection (two), cardiac arrhythmia (two), wound infection (one), prolonged ileus (one), transient confusion (one), self-limiting intra-abdominal haemorrhage secondary to coagulopathy (one),

Table 1 Indications for 133 hepatic resections in 129 patients

Diagnosis	Classical resection	Segmental resection	Operative death
Benign			
Focal nodular hyperplasia	5	1	0
Adenoma	1	0	0
Inflammatory mass (pseudotumour)	4	0	0
Cysts	7	0	0
Cystadenoma	1	0	0
Haemangioma	2	0	0
Biliary stricture	2	0	0
Primary sclerosing cholangitis	3	0	0
Trauma	3	1	1
Intrahepatic stones	1	0	0
Total	29	2	1
Primary malignancy			
Hepatoma (no cirrhosis)	9	0	0
Hepatoma (cirrhosis)	1	3	1
Angiosarcoma	1	0	0
Hepatoblastoma	1	0	0
Clear cell carcinoma	1	0	0
Total	13	3	1
Secondary malignancy			
Colorectal*	50	8	3
Leiomyosarcoma	4	1	0
Carcinoid*	2	1	0
Total	56	10	3
Contiguous tumour			
Gallbladder	0	2	0
Cholangiocarcinoma	16	0	1
Gastric leiomyosarcoma	1	0	0
Adrenocortical carcinoma	1	0	0
Total	18	2	1

*Major classical resection and lesser resection on contralateral side

Table 2 Operative mortality in 133 resections undertaken in 129 patients in relation to type of hepatic resection

Resection	No of resections	Operative deaths
Extended right hepatectomy*	26	2
Extended left hepatectomy	2	0
Right hepatectomy*	54	2
Left hepatectomy	18	0
Left lobectomy	16	1
Trisegmentectomy	4	0
Segmentectomy	11	1
Atypical resection	2	0
Total	133	6

*Major resection and lesser resection on contralateral side

ascites responding to medical therapy (one), prolonged leakage of peritoneal fluid (1), and prolonged postoperative nausea and vomiting (one). Major morbidity occurred in 20 per cent of patients and resulted in prolongation of hospital stay, unplanned radiological or repeat operative intervention, transfer to the intensive care unit or death (Table 4).

Seven patients required further surgical intervention during the same period of hospitalization. Three of the four operations for haemorrhage occurred in the presence of severe coagulopathy related to hepatic failure, and all three patients died. The one patient without coagulopathy survived. One patient developed portal vein thrombosis and required relaparotomy for removal of the thrombus. The patient who had undergone right hepatectomy for major hepatic trauma underwent oversewing of a bleeding duodenal ulcer 6 weeks later, and another patient required repair of a small bowel perforation. Five patients required radiological intervention including percutaneous or endoscopic biliary stent insertion for management of a bile leak (two cases), percutaneous drainage of a subhepatic abscess and an intra-abdominal bile collection (two cases) and placement of a caval filter following thrombolysis of an inferior caval thrombus, the presence of which was noted by intraoperative ultrasonography during hepatic resection for trauma (Table 4).

Five of the six deaths in this series were associated with hepatorenal failure and four of these occurred in non-

cirrhotic patients aged over 60 years. Two of the deaths followed minor resection (Tables 2 and 4).

Late complications

Two patients required further surgery during a subsequent readmission within 1 year of surgery for late complications related to the previous hepatic resection. One patient developed a bronchobiliary fistula and chronic empyema 4 months after an apparently uneventful right hepatectomy for colorectal carcinoma metastases. She made a full recovery following right lower pulmonary lobectomy and hepaticojejunostomy for a common hepatic duct stricture. The other patient underwent revisional hepaticojejunostomy following the development of a left hepatic duct stricture 1 year after extended right hepatectomy and bile duct excision for cholangiocarcinoma. Subsequent histological examination showed this to be due to tumour recurrence, although the patient is alive and symptom-free 30 months after this reintervention. Both of these patients had experienced bile leakage as a complication following hepatic resection but none of the other four patients who developed bile leaks following resectional surgery developed late complications. One of the bile leaks and the late bronchobiliary fistula occurred in two of the three patients in this series who had undergone preoperative chemoembolization.

Survival

The median follow-up for patients resected for malignant disease was 26 months. Survival in patients resected for colorectal metastases was 65 per cent at 3 years. Fourteen patients were alive at 3 years.

Discussion

Most recently published series of hepatic resection have demonstrated an apparent decrease in postoperative mortality rates. Whereas most series have focused on the management of specific hepatic pathology, a few authors have reviewed their entire experience in recent years^{7,13,14}. Comparison with these reports demonstrates an apparent reduction in the indications for hepatic resection for certain pathologies with, for example, a number of workers advocating a more conservative approach to the management of severe liver injury^{15,16}. In the management of benign disease, the continued difficulty of differentiating between adenoma and focal nodular hyperplasia, and of excluding the presence of hepatoma, accounts for the relatively high proportion of patients who have been submitted to resection in this and other series¹³. Only two patients with symptomatic haemangioma underwent resection in the present review, but it is noted that some centres have pursued a much more aggressive approach to the management of this benign pathology¹⁴. Despite the apparent enthusiasm for laparoscopic intervention for hepatic cysts, the present authors have found the need to adopt a more aggressive approach to such lesions. Resection of hepatic cysts in this series was undertaken in patients with recurrence of symptoms following previous laparoscopic and open deroofting of symptomatic disease¹⁷.

Despite the high worldwide prevalence of hepatoma, this tumour comprised only 10 per cent of the resections undertaken in the authors' unit and only 3 per cent of

Table 3 Transfusion requirements for 133 hepatic resections in 129 patients in relation to type of resection

Resection	No. of resections	No. transfused	Median (range) units of blood
Extended right hepatectomy	26	13	1 (0–32)
Extended left hepatectomy	2	2	3 (2–4)
Right hepatectomy	54	23	0 (0–74)
Left hepatectomy	18	7	0 (0–7)
Left lobectomy	16	2	1 (0–4)
Trisegmentectomy	4	2	1 (0–2)
Segmentectomy	11	4	3 (0–3)
Atypical	2	0	0
Total	133	53	0 (0–74)

Table 4 Major hospital mortality and morbidity following 133 hepatic resections in 129 patients

Complication	No. with complication	No. of deaths	Reoperation
Bile leak	8	0	0
Hepatorenal failure	7	5	3
Haemorrhage (without hepatic failure)	3	1	1
Portal vein thrombosis	1	0	1
Inferior vena caval thrombosis	1	0	0
Abscess	1	0	0
Pulmonary embolism	3	0	0
Gastrointestinal haemorrhage	2	0	1
Small bowel perforation or leak	2	0	1
Pneumothorax	1	0	0
Total	29	6	7

resections reported by the Basingstoke group¹¹. Few patients with hepatoma have potentially resectable disease at the time of presentation. In the non-cirrhotic patient, the tumour may have reached a substantial size by the time of presentation, whereas the cirrhotic patient may have compromised liver function sufficient to preclude resection. There has been considerable debate as to whether resection or orthotopic liver transplantation should be considered for such patients¹⁸. The present authors' policy to date has been to consider patients with malignancy for transplantation only if liver dysfunction was the primary indication for hepatic replacement.

There is increasing acceptance in Europe and North America that patients with metastatic spread of tumour to the liver may benefit from hepatic resection^{19,20}. Reduced morbidity and mortality rates have been reported in large series, and this has translated into significant long-term survival in a patient population in whom survival at 5 years without resection is exceptional¹⁹. Follow-up of the present group of patients is still limited, but the authors are encouraged by the 3-year survival rate of 65 per cent in patients who underwent resection of colorectal metastases. It is clear that patients with other metastatic disease may also benefit from resection. Contiguous tumour and tumours arising from the gallbladder and extrahepatic bile ducts may also be amenable to resection^{9,20}, although there is the potential for greater morbidity and the long-term outlook for these patients is less encouraging. None the less, a more aggressive approach to the management of cholangiocarcinoma in recent years has been associated with improved long-term survival and quality of life²¹.

Recent reports have consistently highlighted improved perioperative morbidity and mortality rates following hepatic resection. The careful selection of patients and the use of laparoscopic and intraoperative ultrasonography in the authors' unit have ensured that patients with hepatic malignancy are submitted to laparotomy only with the intent of effecting surgical cure²². Despite the use of advanced resection techniques, substantial complications may result, and the risks to the patient should not be underestimated. In the cirrhotic patient, attempts have been made to define postoperative risk but this may be difficult to determine for an individual patient. Various investigators have identified risk factors, which include preoperative alkaline phosphatase determination²³, age, volume of parenchymal resection, and hepatic function as measured by oral glucose tolerance or indocyanine green dye retention rate²⁴. The importance of minimizing blood loss has been stressed by other workers^{6,11}. Jamieson and colleagues⁶ associated longer operating time with an increased need for transfusion, whereas others have reported significantly shorter operating times associated with a greater transfusion requirement than that reported in the present series^{25,26}. While a number of factors, including the extent of resection, may determine the requirement for transfusion, there would appear to be considerable logic in minimizing blood loss¹³.

In some centres a more radical approach to the management of hepatic malignancy has been advocated. There is increasing evidence that some patients who develop recurrent hepatic tumour following previous resection of colorectal metastasis will benefit from further hepatic resection²⁷⁻²⁹. The development of techniques employing total vascular exclusion of the liver^{10,30} and *ex vivo* resection^{31,32} has enabled removal of lesions that were

previously thought to be irresectable by conventional techniques. In this series, vascular exclusion was not employed in any case, and others have cautioned against the excessive use of total vascular exclusion, suggesting that blood loss may be increased during caval dissection which confers no advantage during less major hepatic resections^{31,33}.

Hepatic resection is well established in the management of a number of benign and malignant hepatobiliary pathologies but it would seem desirable that hepatic surgery be undertaken only in specialist centres. Post-operative deaths in this series were attributable largely to the development of hepatic failure and occurred only in patients with trauma or malignancy. Future identification of perioperative risk factors may improve the safety of hepatic resection.

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Announcement

Frank Glenn Travelling Fellowship 1998

The International Hepato-Pancreato Biliary Association invites applicants for the above Fellowship. An award of SFr10000 (ten thousand Swiss Francs) is available to subsidize a young investigator in the field of hepatic, biliary or pancreatic research. The Fellowship is intended to support travel outside the person's country connected with research purposes. Applicants should be under 40 years of age and should have at least one publication on aspects of HPB disease. Applications should be made in writing and should include the following:

- A copy of the applicant's *Curriculum Vitae*
- One (A4) page summary of the relevant research describing how the award is to be used. Preference will be given to applicants intending to use the Fellowship to support their own participation in research. Therefore, an outline of the research and the role to be played by the applicant should be detailed.
- A letter of nomination from either a Member of the IHPBA or the Chairman of the applicant's department (who need not be a Member).
- A letter of support from the supervisor in the department where the applicant is to work.

Applications should be sent by 27 March 1998 to:

Professor J. Toouli, Gastrointestinal Surgical Unit, Department of Surgery, Flinders Medical Centre, Bedford Park, Adelaide, South Australia, Australia 5042. Tel: (618) 8204 5213; Fax: (618) 8204 5966; Email: Jim.Toouli@flinders.edu.au

The name of the successful applicant will be announced at the IHPBA World Congress in Madrid, Spain, 24–28 May 1998. It is expected that the applicant will submit the results of their research for presentation at the World Congress in Brisbane in 2000.

Prediction of resectability of pancreatic malignancy by computed tomography

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Background The accuracy of computed tomography (CT) in predicting resectability of pancreatic malignancy has been questioned recently and alternative methods have been recommended.

Methods To determine the accuracy of CT for predicting resectability and its influence on survival, a standard protocol for performing CT and reporting the results was developed and then compared retrospectively with the ability of one surgeon to perform a resection during 1989–1994. Postoperative survival was determined.

Results Of 88 consecutive patients 35 (40 per cent) had CT-resectable disease and 53 (60 per cent) had CT-irresectable disease. Twenty-one patients were excluded because of advanced disease or poor performance status. Of the remaining 67 patients, 47 (70 per cent) had pancreatic ductal adenocarcinoma and 20 (30 per cent) had ampullary adenocarcinoma, of whom 32 had a resection, 32 had a palliative bypass and three had only a staging laparoscopy. The sensitivity and specificity for computed tomographic prediction of resectability were 72 and 80 per cent respectively. The positive predictive value was 77 per cent and the negative predictive value 76 per cent. There were seven false-positive and nine false-negative findings. Survival was more dependent on whether or not resection was performed than on computed tomographic predictability of resection.

Conclusion CT was reasonably accurate in predicting resectability but cannot be relied on entirely, requiring an improvement in staging methods for pancreatic malignancy.

Pancreatic ductal adenocarcinoma is a leading cause of death^{1–4}, accounting for 3 per cent of all cancers and 5 per cent of all deaths from cancer⁵. Following resection 5-year survival rates are of the order of 10–24 per cent^{6–9}. Ampullary adenocarcinoma is much less common but is resectable more frequently, following which the 5-year survival rate is 30–60 per cent^{8–10}. Pancreatoduodenectomy has been associated with high morbidity and mortality rates in the past^{11–13} but the results have improved dramatically in recent years with operative mortality rates of around 5 per cent in specialist units^{8, 14–19}.

Surgical exploration has been recommended by some authors for most patients with pancreatic ductal adenocarcinoma either with a view to resection^{20–23} or palliative bypass²³, but only 10–20 per cent of tumours are resectable^{19–22}. With the increased availability of percutaneous and endoscopic biliary stenting as well as laparoscopic methods of bypass^{24, 25}, it has become more important to identify patients with irresectable disease before therapeutic intervention.

Computed tomography (CT) has become an important method for preoperative staging^{26–35}. Several studies have suggested, however, that CT alone is too inaccurate for the evaluation of resectability in pancreatic ductal adenocarcinoma and should be used in conjunction with other investigations such as angiography and staging laparoscopy or laparoscopic ultrasonography^{26, 33, 36, 37}. So far, magnetic resonance imaging has proved not to be superior to CT in determining the resectability of pancreatic malignancy^{38, 39}. Positron emission tomography appears to be effective at demonstrating lymph node and liver metastases but needs to be investigated more

thoroughly with regard to its value in assessing resectability^{40, 41}.

In view of the conflicting data and the absence of any studies from the UK, the ability of CT to predict tumour resectability in patients with a diagnosis of pancreatic malignancy was investigated.

Patients and methods

The aims of this study were: (1) to compare the accuracy of CT in predicting resection of pancreatic malignancy (pancreatic ductal adenocarcinoma and ampullary adenocarcinoma); and (2) to assess survival according to the computed tomographic findings and whether or not surgical resection was performed.

Study design

Consecutive patients with pancreatic ductal adenocarcinoma and ampullary adenocarcinoma referred to a single consultant pancreatic surgeon (J.P.N.) were studied. Over an 18-month period a standard radiological protocol for CT (see below) was developed with an identified consultant pancreatic radiologist (G.S.). In addition to CT, all patients underwent endoscopic retrograde cholangiopancreatography. Following this preliminary 18-month period, the study was commenced in 1989 and completed in 1994. Most of the computed tomographic examinations were reported by G.S. and, in his absence, by two other consultant radiologists familiar with the protocol (see Acknowledgements). The tumours were assessed for resectability following a standard protocol and were labelled as resectable or irresectable. The computed tomographic images were discussed jointly between the radiologist and surgeon before and after operation. To standardize for the gain in radiological expertise, at the end of the study all the computed tomograms were again reviewed retrospectively by the principal pancreatic radiologist (G.S.) and used for the final analysis. The names of the patients were cross-checked between the records held independently in the departments of surgery and radiology. No other method of

preoperative staging was used (such as selective angiography) except for laparoscopy in highly selected cases.

All patients had the diagnosis confirmed by histological examination of tissue obtained by percutaneous biopsy, endoscopic biopsy or open biopsy, or by examination of the resected specimen. Histological assessment of the resection specimens included the type and size of the primary tumour, lymph node involvement, tumour grade and any involvement of the resection margins. All patients were followed prospectively. A census was undertaken 18 months after the last patient underwent laparotomy.

For computed tomographic criteria of resectability, the data for both types of pancreatic malignancy were combined, as these are the same criteria²⁶⁻²⁸. Because of differences in survival between patients with pancreatic ductal adenocarcinoma and ampullary adenocarcinoma⁶⁻¹¹, these were analysed separately. For each tumour type survival was analysed according to four groups: group 1, CT-resectable and resection performed; group 2, CT-irresectable and resection performed; group 3, CT-irresectable and no resection performed; and group 4, CT-resectable and no resection performed.

Performance and reporting of computed tomography

Abdominal computed tomographic images were produced using a Siemens Somatom Hi Q scanner (Siemens, Erlangen, Germany). All patients were given a rapid intravenous bolus of 100 ml of Niopam 300 contrast medium (Merck Pharmaceuticals, Middlesex, UK) in addition to oral contrast medium. Following injection of contrast, 3–5-mm slices were taken with patients holding their breath. Analysis involved evaluation of the following: (1) local tumour extension; (2) partial or complete vessel encasement of major arteries and veins surrounding the pancreas (the superior mesenteric–portal venous system and the superior mesenteric, splenic and hepatic arteries); (3) the presence or absence of liver metastases; (4) lymphadenopathy of localized and regional lymph nodes; (5) the size of the pancreatic mass; and (6) regional organ invasion, notably the stomach, colon, duodenum, small bowel mesentery and spleen. The computed tomographic criteria for surgical irresectability were one or more of the following: (1) extension beyond the dorsal pancreatic fascia; (2) partial or complete encasement of the superior mesenteric–portal venous system; (3) partial or complete encasement of the superior mesenteric or hepatic arteries; (4) the presence of liver metastases; (5) local organ invasion other than the prepyloric region of the stomach or duodenum; and (6) regional lymphadenopathy in the case of pancreatic ductal adenocarcinoma but not ampullary adenocarcinoma.

Selection for operation

Patients were excluded from any surgical intervention for one or both of the following reasons. (1) the patient was not fit for major surgical intervention because of significant comorbidity; and (2) CT revealed disease comprising liver metastases and/or higher lymphadenopathy or a tumour 5 cm or more in diameter with multiple vessel encasement and/or invasion into adjacent organs other than the duodenum.

Performance of operation

At laparotomy the criteria for irresectability were: (1) hepatic or peritoneal metastases; (2) invasion of the tumour directly into nearby organs other than the duodenum or the prepyloric gastric region; (3) complete or partial encasement of the superior mesenteric or hepatic arteries; and (4) regional lymphadenopathy confirmed on frozen section in the case of pancreatic ductal adenocarcinoma, but not ampullary adenocarcinoma. Partial encasement of the superior mesenteric–portal venous system was not a contraindication to a trial dissection of the tumour⁴². In the absence of overt evidence of advanced disease at laparotomy, all patients had a trial dissection with a view to resection. If this was not possible a palliative bypass procedure was performed.

Indications for laparoscopy

Preoperative staging laparoscopy was not performed routinely. Only patients whose tumour was deemed to be resectable by the original CT report but who were judged to have advanced disease on clinical judgement, especially in the presence of marked weight loss, unremitting back pain or a palpable abdominal mass, underwent laparoscopy.

Adjuvant treatment

As part of the UK Pancreatic Cancer Group Adjuvant Combined Treatment Study (UKPACA-1) all patients with pancreatic cancer received postoperative radiotherapy (40 Gy) in 20 fractions over 4 weeks and 5-fluorouracil 500 mg/m² given as an intravenous bolus weekly for 6 months⁴³.

Statistical analysis

Categorical data were analysed with the two-tailed Fisher's exact probability test. Cumulative survival rates were calculated with the Kaplan–Meier method and differences in survival were analysed by the Mantel–Haenszel log rank test. Cumulative survival curves and statistical calculations included all deaths after any procedure, including in-hospital deaths. $P < 0.05$ was considered statistically significant.

Results

Eighty-eight patients presented during the period of the study. Following radiological assessment 35 patients (40 per cent) were categorized as surgically resectable and 53 (60 per cent) were deemed surgically irresectable. Twenty-one of the 88 patients were excluded from further analysis. In 16 patients this was because of advanced disease and poor performance status. Of these, 15 had multiple vessel encasement, 12 had liver metastases, ten had dorsal space extension, eight had a primary tumour 5 cm or more in diameter, four had hilar lymphadenopathy and four had invasion into the stomach. The other five patients were deemed to have resectable disease on computed tomographic criteria but were not fit enough to undergo major surgery. These 21 patients were treated non-surgically, which included the use of endoscopic and radiological stenting. A direct comparison between computed tomographic findings and surgical exploration was undertaken in the remaining 67 patients, of whom 47 had ductal adenocarcinoma of the pancreas and 20 had ampullary adenocarcinoma. There were 41 men and 26 women with a median age of 66 (range 33–79) years and 62 (range 35–80) years respectively. The type of operation performed is shown in Table 1. There was no significant difference in the resectability rate between pancreatic ductal and ampullary adenocarcinoma ($P = 0.11$). Thirty-two patients underwent curative resection (30 had a Kausch–Whipple procedure and two had total pancreatectomy), 32 underwent a bypass

Table 1 Operations for pancreatic ductal and ampullary adenocarcinoma in 67 patients

Operation	Pancreatic cancer (<i>n</i> = 47)	Ampullary cancer (<i>n</i> = 20)	Total (<i>n</i> = 67)
Resection	19	13	32
Bypass procedure	25	7	32
Laparoscopy alone	3	0	3

procedure and three patients had staging laparoscopy only. The median time from the staging CT to operative intervention was 8 (range 3–13) days. After curative resection, histological examination demonstrated that 19 tumours were pancreatic ductal adenocarcinomas, 18 of which were in the head of the pancreas and one was in the mid-body of the gland, and the remaining 13 were ampullary adenocarcinomas.

The relationship between computed tomographic prediction of resectability and outcome following surgical assessment is shown in Table 2. For tumours labelled by CT as surgically resectable, there were seven false positives. Three of these were the patients who had undergone staging laparoscopy because of clinical suspicion of irresectability (in two because of marked cachexia and in one because of a palpable abdominal mass that was not apparent on CT). Laparoscopy demonstrated invasion of the tumour through the transverse mesocolon in one patient, liver metastases in another, and both liver and peritoneal metastases in the third. The other four patients had irresectable tumours: portal lymphadenopathy positive for tumour cells in two patients with ductal adenocarcinoma; liver metastases in one patient; and superior mesenteric artery encasement in one. Six of the seven patients had cancer of the head of the pancreas and one had ampullary cancer.

There were nine false predictions of irresectability (Table 3). Five patients with vessel encasement on computed tomographic assessment all had a tumour that abutted the vessel wall and was dissected clear of the vessel wall. In a further five cases, all with pancreatic ductal adenocarcinoma, partial venous encasement was found at laparotomy even though the computed

tomographic assessment was reported as normal in this respect. In three cases the superior mesenteric vein and in two the hepatic portal vein was partially excised (Subsequent analysis showed that there was no difference in survival between patients undergoing partial venous excision and those who did not require this technique as part of the resection.)

The accuracy of CT in determining liver metastases, vessel encasement, dorsal pancreatic space extension and lymphadenopathy is shown for pancreatic ductal and ampullary carcinomas combined in Table 4. Overall, CT was 72 per cent sensitive and 80 per cent specific for predicting resectability, with a positive predictive value of 77 per cent and a negative predictive value of 76 per cent.

The cumulative survival rates for the 47 patients with pancreatic ductal adenocarcinoma analysed according to whether or not they underwent resection are shown in Fig. 1. Median survival for the 15 patients who had CT-resectable disease and who underwent resection (group 1) was 313 (95 per cent confidence interval (c.i.) 94–326) days, compared with 273 (95 per cent c.i. 150–662) days for the four who had CT-irresectable disease but still had a resection (group 2) (P not significant). Median survival was 85 (95 per cent c.i. 79–184) days for the 22 patients who had CT-irresectable disease and did not undergo resection (group 3), compared with 27 (95 per cent c.i. 10–110) days for the six who had CT-resectable disease but had no resection (group 4) (P not significant). There was a significant difference in survival between patients who had a resection (groups 1 and 2) and those who did not (groups 3 and 4) ($\chi^2 = 16.4$, 1 d.f., $P < 0.005$). Similar results were demonstrated for patients with ampullary cancer (data not shown).

There were no 30-day or in-hospital deaths following resection, irrespective of the tumour type or computed tomographic findings. The median length of survival following resection for pancreatic ductal adenocarcinoma was 11 (95 per cent c.i. 7.6–14.4) months; following bypass it was 89 (95 per cent c.i. 37–141) days ($\chi^2 = 15.5$, 1 d.f., $P < 0.005$). For ampullary cancer the median survival time was 21 (95 per cent c.i. 15–26) months following resection and 90 (95 per cent c.i. 34–147) days following bypass ($\chi^2 = 14.6$, 1 d.f., $P < 0.005$). Survival of patients who had a resection was longer in those with ampullary cancer than in those with pancreatic ductal adenocarcinoma ($\chi^2 = 5.77$, 1 d.f., $P < 0.025$), but there was no significant difference in survival between these groups of patients following bypass surgery.

Five of the 32 patients who underwent resection had positive resection margins: four had ductal adenocarcinoma and one had ampullary adenocarcinoma. Analysis by cancer type did not show any significant difference in survival time between those with positive or

Table 2 Computed tomographic assessment of surgical resectability and irresectability *versus* outcome following surgical assessment

CT assessment of adenocarcinoma	No. of patients (n = 67)	Surgical outcome	
		Curative resection (n = 32)	Palliative procedure (n = 35)
Resectable			
Pancreatic ductal	21	15	6
Ampullary	9	8	1
Total	30	23	7
Irresectable			
Pancreatic ductal	26	4	22
Ampullary	11	5	6
Total	37	9	28

CT, computed tomographic

Table 3 Reasons for computed tomographic irresectability in nine patients who underwent curative resection

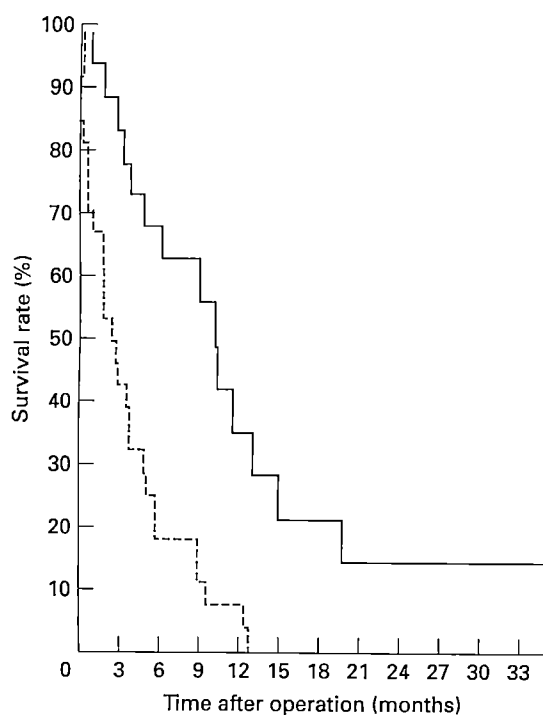
Tumour type	CT assessment				
	Vessel encasement		Dorsal pancreatic space extension	Lymphadenopathy	Any combination
	SMA	SMV			
Pancreatic cancer (n = 4)	0	2	4	1	3
Ampullary cancer (n = 5)	2	1	2	NA	2
Total (n = 9)	2	3	6	1	5

CT, computed tomographic; SMA, superior mesenteric artery; SMV, superior mesenteric vein; NA, not applicable

Table 4 Positive and negative predictive values for separate computed tomographic criteria in staging pancreatic malignancy

Criterion for local cancer spread	Positive predictive value*	Negative predictive value*
Liver metastasis	5 of 5 (100)	59 of 62 (95)
Venous encasement	6 of 11 (55)	53 of 56 (95)
Arterial encasement	16 of 17 (94)	47 of 50 (94)
Dorsal pancreatic space extension	27 of 33 (82)	34 of 34 (100)
Lymphadenopathy†	10 of 11 (91)	35 of 36 (97)

Values in parentheses are percentages. *Number of cases with positive (or negative) findings on computed tomography (CT) that were confirmed on surgical assessment of the total number of cases with CT-positive (or negative) findings. †Applicable only to patients with pancreatic ductal adenocarcinoma



No. at risk

Resection	19	16	13	12	11	5	4	3	3	3	3
No resection	28	12	5	3	2	0	0	0	0	0	0

Fig. 1 Cumulative survival rates of 47 patients with pancreatic ductal adenocarcinoma analysed according to surgical procedure performed. —, Survival in the 19 resected cases; ---, survival in the 28 non-resected cases

clear resection margins. Lymph nodes with metastases were present in 15 of 19 patients with pancreatic ductal adenocarcinoma and in six of 13 with ampullary adenocarcinoma. No significant survival difference was demonstrated according to lymph node status when analysed by tumour type (data not shown).

Discussion

In this study CT was a reasonable predictor of resectability for pancreatic ductal and ampullary adenocarcinomas and was accurate at demonstrating liver

Table 5 Positive and negative predictive values of computed tomography in the assessment of resectability of pancreatic malignancy from the present study and previously published data

Series	Year	Positive predictive value*	Negative predictive value†
Andersen <i>et al.</i> ²⁶	1993	16 of 25 (64)	19 of 27 (70)
Freeny <i>et al.</i> ²⁹	1988	7 of 9 (78)	38 of 42 (90)
Itai <i>et al.</i> ³¹	1982	13 of 25 (52)	40 of 41 (98)
Levitt <i>et al.</i> ³²	1982	9 of 10 (90)	157 of 160 (98)
Warshaw <i>et al.</i> ³³	1990	14 of 31 (45)	22 of 24 (92)
Savarino <i>et al.</i> ³⁴	1983	18 of 22 (82)	19 of 22 (86)
Ross <i>et al.</i> ³⁵	1988	9 of 24 (38)	39 of 42 (93)
Present study	1998	15 of 21 (71)	22 of 26 (85)

Values in parentheses are percentages. *Number of cases shown to be resectable on computed tomography (CT) and at laparotomy of the total number that were CT-resectable; †number of cases shown to be irresectable on CT and at laparotomy of the total number that were CT-irresectable

metastases, vessel encasement, dorsal pancreatic space extension and lymphadenopathy. The positive predictive value of CT for resectability was 77 per cent and the negative predictive value was 76 per cent (71 and 85 per cent respectively for pancreatic ductal adenocarcinoma), results that compare favourably with those of previous studies^{26,29,31-35} (Table 5). This accuracy may be improved on by the use of better-resolution CT scanners using spiral CT, which have become widely available since this study was completed. Although this and other series^{26,32,34} have demonstrated high positive and negative predictive values for CT in determining resectability, several other studies have shown relatively poor results^{25,31,33,35}, prompting the use of alternative methods of preoperative staging.

Laparoscopy is valuable at demonstrating peritoneal and liver metastases that have not been identified on CT^{33,44} and several groups^{36,45-47} have confirmed the value of laparoscopy and laparoscopic ultrasonography in determining resectability. Given the fact that all the patients undergoing staging laparoscopy in these studies must have undergone previous radiological assessment, the resection rates were surprisingly low (26–56 per cent) and compare unfavourably with the sensitivity of 72 per cent or more for CT in predicting resectability in this and other studies^{29,32,34}. A number of factors may account for the discrepancy in the accuracy of preoperative radiological staging between studies advocating the routine use of laparoscopy and those reporting excellent results from CT, including the referral pattern to the surgeon, the quality of radiological imaging, the independent skills of the radiologist and surgeon, and, equally importantly, the interaction of these specialists. The role of laparoscopy and laparoscopic ultrasonography in preoperative staging needs to be defined further as, if high-quality CT is available, the majority of laparoscopic procedures would not reveal advanced disease in cases deemed to be resectable.

It has been the authors' policy that all medically fit patients who have CT-resectable pancreatic tumour should undergo a trial dissection. If patients have CT-resectable tumours but clinical signs of advanced disease (cachexia, back pain and inexplicable abdominal masses), they undergo staging laparoscopy. Even though the computed tomographic images were reviewed retrospectively to take into account the gain in radiological expertise during the course of the study, several of the CT

criteria for irresectability could still be judged only as relative, especially in cases of venous encasement, dorsal pancreatic space extension and lymphadenopathy. This is illustrated by the nine false-negative predictions when curative resection was performed. Interestingly, the worst computed tomographic criterion for determining irresectability was venous encasement, with a positive predictive value of only 55 per cent. Therefore, some of the radiological criteria used to determine irresectability need further review. For example, the degree of venous encasement may need to be clarified further according to the position, length and proportion of the circumference involved. The objective should be to define a borderline group that might benefit from laparoscopy and laparoscopic ultrasonography, but this will need to be assessed in a prospective study.

Cumulative survival rates for patients with pancreatic ductal or ampullary adenocarcinoma undergoing resection or bypass were comparable to those found in previous studies⁸. For the 47 patients with pancreatic ductal adenocarcinoma, cumulative survival rates were analysed according to computed tomographic findings and surgical outcome. Patients who underwent resection irrespective of the computed tomographic prediction of resectability had a similar cumulative survival rate and, similarly, there was no statistical difference in survival between the two groups of patients who could not undergo resection. Thus the false-negative findings on CT did not influence survival. Analysis by cancer type did not show any significant difference in survival time between those with positive or clear resection margins or for lymph node status. This is contrary to the expected findings, as negative lymph nodes and clear resection margins have been shown to be predictors of longer survival⁴⁸⁻⁵⁰. The present findings may be attributable to all of the patients being enrolled into the UKPACA-1 study and receiving adjuvant therapy⁴³, which may have conferred a survival advantage⁵¹.

In summary, CT was found to be a good predictor of resectability for pancreatic malignancy, but the criteria for irresectability need to be refined further by prospective study. This may help to establish which patients might benefit from further preoperative staging such as laparoscopy or laparoscopic ultrasonography.

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Bile duct obstruction due to portal biliopathy in extrahepatic portal hypertension: surgical management

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Background Varices can develop in and around the bile duct in the presence of portal hypertension, especially when it is caused by extrahepatic portal vein thrombosis. The term 'portal biliopathy' is used to describe changes in the bile duct due to these varices, which may cause bile duct obstruction. This paper reviews experience of the surgical management of patients with symptomatic portal biliopathy.

Methods Nine patients with extrahepatic portal vein obstruction with symptomatic portal biliopathy were reviewed retrospectively.

Results Eight patients presented with jaundice, two had abdominal pain and one had recurrent cholangitis. Endoscopic retrograde cholangiography revealed abnormality of the bile duct wall, with stricture in eight patients and bile duct calculi in two. Portasystemic shunting relieved jaundice in five of seven patients, and in two a second-stage hepaticojejunostomy was required.

Conclusion Symptomatic biliary obstruction in patients with extrahepatic portal hypertension may be relieved by a portasystemic shunt. Rarely biliary bypass may be required and is rendered safer by previous portasystemic shunting to decompress the pericholedochal varices. A direct approach to the biliary tract without a preliminary shunt may be hazardous and is frequently unnecessary.

Extrahepatic portal vein obstruction (EHPVO) is a common cause of portal hypertension in India and most commonly manifests as bleeding from oesophagogastric varices. Occlusion of the portal vein results in the formation of hepatopetal collaterals within the hepatoduodenal ligament and in the bile duct. These periportal and pericholedochal varices may exert extrinsic pressure on the bile duct and produce changes in its contour and outline. The term 'portal biliopathy' has been used to describe abnormalities of the extrahepatic and intrahepatic bile ducts in patients with portal hypertension, especially those with EHPVO¹. A majority of these patients are asymptomatic, but occasionally there is symptomatic bile duct obstruction. This paper reports experience of nine patients of EHPVO who required surgical management for biliary obstruction due to portal biliopathy.

Patients and methods

Between January 1987 and December 1995, 210 patients with EHPVO were referred for various complications related to portal hypertension. The diagnosis of EHPVO was confirmed by the presence of splenomegaly, oesophagogastric varices on endoscopy and ultrasonographic evidence of a recanalized or blocked portal vein replaced by a portal cavernoma. Nine (4 per cent) of these patients were referred for surgical intervention for symptoms of bile duct obstruction. The records of these patients were reviewed and form the basis of this report.

Results

There were seven men and two women of mean age 21 (range 18–36) years. No cause of EHPVO could be

established in any patient and none had undergone intra-abdominal surgery in the past. Five patients had gastrointestinal bleeding which had been managed successfully by endoscopic sclerotherapy. The other four patients had grade I–II oesophageal varices but had never bled. Eight patients presented with jaundice, two had abdominal pain and one patient had recurrent attacks of cholangitis.

The levels of serum bilirubin (range 2.2–9.6 mg/dl) and alkaline phosphatase (range 310–1100 units) were raised in all nine patients. Ultrasonography showed normal echogenicity of the liver; the portal vein could not be seen in any patient and was replaced by anechoic tubular structures. In six patients the bile duct could not be identified. Dilatation of the bile duct in the region of the porta hepatis was seen in three patients, two of whom had multiple calculi, the duct being surrounded by multiple tortuous collaterals. The gallbladder was distended in three patients and had multiple overlying collaterals, but no patient had gallstones.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all patients and irregularity of the outline of the bile duct was the commonest finding (Fig. 1). Seven patients had a stricture in the bile duct (Fig. 2) and one had multiple calculi proximal to the stricture (Fig. 3). Another patient had multiple calculi with no demonstrable stricture and had undergone endoscopic sphincterotomy with extraction of bile duct stones 2 years earlier (Table 1).

At laparotomy these patients had a normal-looking liver but the hepatoduodenal ligament was thick, fibrotic and covered by multiple tortuous veins. In none of the patients could the common bile duct be visualized separately, although stones were palpable in two cases. The gallbladder was covered with multiple collaterals and no patient had gallstones. In two early patients an attempt to approach the bile duct directly and drain it into



Fig. 1 Endoscopic retrograde cholangiogram showing irregularity of the bile duct wall

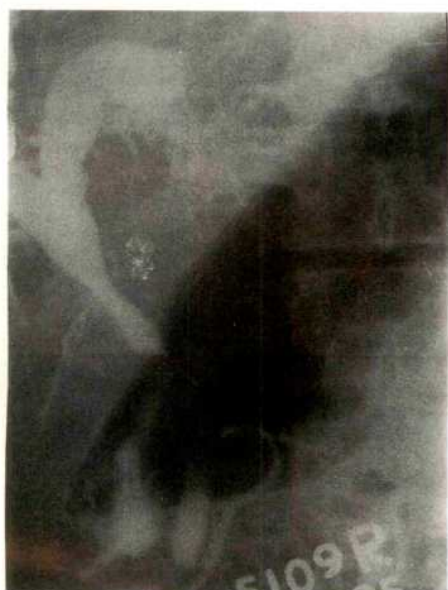


Fig. 2 Endoscopic retrograde cholangiogram showing a stricture in the infracystic part of the common bile duct

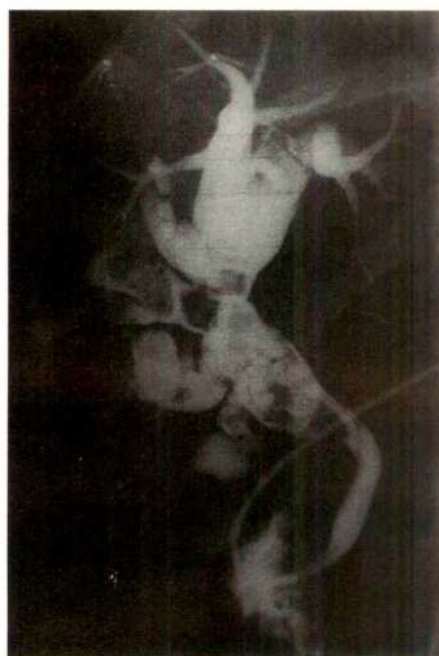


Fig. 3 Cholangiogram showing a stricture in the bile duct with multiple intrahepatic stones

jejunum resulted in excessive bleeding, and one patient died after operation. The other patient developed narrowing of the choledochojejunostomy stoma and had recurrent cholangitis. Endoscopic stenting of the native bile duct was performed but stent removal after 9 months was associated with the reappearance of jaundice and cholangitis. The patient was advised to undergo portasystemic shunting, but refused and was lost to follow-up.

Seven patients underwent portasystemic shunting (splenectomy and splenorenal anastomosis) (Table 1). Patients with multiple calculi in the bile duct underwent endoscopic sphincterotomy and stone extraction 6 weeks after portasystemic shunting. Regression of jaundice and a fall in serum bilirubin and alkaline phosphatase levels was seen in five patients within 3–7 weeks of surgery. In two patients jaundice and raised serum alkaline phosphatase levels persisted despite a patent splenorenal shunt, confirmed by endoscopic evidence of regression in grade of oesophageal varices and ultrasonography showing disappearance of the pericholedochal collaterals. Doppler ultrasonography also confirmed a patent shunt, and repeat ERCP in these patients showed persistence of the stricture in the common bile duct. After 6 months of portasystemic shunting, re-exploration in these two patients revealed minimal varices in the hepatoduodenal

Table 1 Cholangiographic findings and operative procedures in nine patients with symptomatic portal biliopathy

ERCP findings	No. of patients	Operative procedure	Outcome and subsequent procedure
Bile duct stricture	7	Choledochojejunostomy (2)	Anastomotic narrowing (1)
		Portasystemic shunt (5)	Died (1)
			Recovered (3)
Bile duct stricture and calculi	1	Portasystemic shunt	Staged hepaticojejunostomy (2)
Bile duct calculi	1	Portasystemic shunt	Endoscopic sphincterotomy and stone extraction
			Endoscopic sphincterotomy and stone extraction

ERCP, endoscopic retrograde cholangiopancreatography

ligament, and access to the bile duct was easy. A fibrous stricture was present in the mid common bile duct and a Roux-en-Y hepaticojejunostomy was carried out, jaundice being relieved in both patients within 2 weeks of surgery.

Liver biopsy in all patients showed normal liver morphology. Bile cultures taken during surgery were sterile in six patients and in the two patients with common bile duct stones *Escherichia coli* was isolated. All patients had normal liver function during follow-up.

Discussion

Patients with EHPVO are known to have a high frequency of duodenal, rectal and other ectopic varices². Pericholedochal and periportal varices are also more commonly observed in the presence of portal vein obstruction because of the greater number of collaterals developing to bypass the near-total occlusion of the portal vein and also because the occlusion occurs in youth, giving rise to a prolonged stimulus for collateral formation.

The extrahepatic bile duct is surrounded by two venous systems: the paracholedochal veins of Petren³, which run parallel to the duct wall, and the epicholedochal plexus of Saint⁴, which is on the surface of the bile duct. Dilatation of these veins produces extrinsic impressions and irregular mural defects in the common bile duct wall^{5,6}. Dilawari and Chawla⁷ studied 20 patients with EHPVO, and on ERCP found changes resembling sclerosing cholangitis in all patients. The presence of focal narrowing and dilatation of the bile duct was thought to be due to extrinsic pressure by the pericholedochal collaterals. Khuroo *et al.*⁸ observed angulation and displacement of ducts in addition to the presence of strictures, calibre changes and extraluminal impressions on the bile duct. They ascribed the former changes to fibrous scarring in the porta hepatitis. Similar changes have also been labelled as the 'pseudocholangiocarcinoma sign'⁹. Patients with cirrhosis may also show such signs when thrombosis of the portal vein occurs¹⁰. Although cholangiographic features of portal biliopathy have been seen in nearly all patients with EHPVO, few are symptomatic because the changes in a majority of patients are patchy and diffuse, but once dominant strictures or bile duct stones have developed symptoms appear.

Symptomatic patients are usually adults, indicating that portal biliopathy is a progressive disease. Biliary obstruction in these patients manifests either as jaundice, abdominal pain or cholangitis, jaundice being the commonest presentation in this series. In patients with EHPVO jaundice is seen infrequently. Webb and Sherlock¹¹ reviewed 97 patients with EHPVO; 13 had raised levels of serum bilirubin, six of whom had gastrointestinal bleeding, two had intermittent jaundice and five persistent jaundice.

Previous reports of bile duct varices have focused mainly on the risk of excessive haemorrhage during surgery on the bile ducts, the chances of haemobilia during percutaneous transhepatic cholangiography and the possibility of mistaking a dilated varix for the bile duct^{6,12,13}. There are also case reports of jaundice caused by the pressure of the pericholedochal varices on the bile duct^{14,15}, as the pressure in these veins is higher than that in the bile duct. Obstructive jaundice caused by a portal cavernoma has been reported to be relieved by a portasystemic shunt¹⁶, as in this series. Direct approach to the common bile duct in the presence of varices in the

hepatoduodenal ligament leads to profuse bleeding and should be attempted only after previous portasystemic shunting has allowed regression of varices¹⁷. In a recent report¹⁰, regression of bile duct changes has also been reported following transjugular intrahepatic portasystemic shunting in patients with cirrhosis. In the present series bile duct obstruction persisted in two patients despite a patent portasystemic shunt, indicating that pressure on the common bile duct by varices may not be the sole mechanism producing changes in the bile ducts. Fibrosis in the pericholedochal area may be an additional reason for continued obstruction, as proposed by Khuroo *et al.*⁸ to explain the ERCP features of displacement and angulation of bile duct. This fibrosis may have occurred as a reaction to the infectious process that caused thrombosis of the portal vein. Bile duct strictures in these patients with EHPVO were ascribed to portal biliopathy as none of them had had any biliary tract surgery in the past, nor were there stones in the gallbladder of any patient that could produce a Mirizzi type of inflammation.

Choledocholithiasis in patients with portal biliopathy associated with EHPVO is rare and can be managed by endoscopic sphincterotomy¹⁸. Two patients in the present series had stones in the bile duct in the absence of gallstones; the presence of biliary abnormality on cholangiography was indicative of a potential role for biliary stasis. Although the calculi can be removed by endoscopic sphincterotomy, the biliary obstruction remains unrelieved and chances of recurrent stones remain high; portasystemic shunting is required as a definitive procedure to relieve the biliary stasis and prevent further stone formation.

Endoscopic sclerotherapy and portasystemic shunting are both effective procedures in managing variceal bleeding in patients with EHPVO. The authors believe that a shunt is preferable because it provides definitive treatment to a young patient with an otherwise normal life expectancy. An additional benefit is that the shunt decompresses the bile duct varices as well, whereas with sclerotherapy the varices continue to enlarge and may produce portal biliopathy. The authors now regard symptomatic portal biliopathy as one of the few indications for portasystemic shunting in the absence of variceal bleeding.

In patients with EHPVO, symptomatic biliary obstruction by portal biliopathy, although uncommon, is a challenging problem. Total portasystemic shunts cause regression of varices in and around the bile duct and usually relieve the choledochal obstruction. In some patients with long-standing disease, hepaticojejunostomy may be needed to treat the biliary obstruction, access to the region being made possible by an initial portasystemic shunt.

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Laparoscopic drainage of liver abscesses

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Background The mainstay of the management of liver abscesses has been intravenous antibiotics and radiologically guided percutaneous drainage. However, not all abscesses are treated successfully in this way, and some require surgical drainage. Laparoscopic drainage of liver abscesses may be an alternative to open surgical drainage.

Methods Twenty consecutive patients with liver abscesses treated by laparoscopic drainage in combination with intravenous antibiotics were studied prospectively. Fifteen had had failed percutaneous drainage previously

Results There were 13 right lobe and seven left lobe abscesses ranging from 6 to 25 cm in diameter. Mean operating time was 38 min. Seventeen patients were drained successfully. Three patients developed recurrent symptoms of which two resolved with conservative measures, but one required a second laparoscopic procedure. There were no intraoperative or other postoperative complications in the 20 patients. Follow-up ranged from 5 to 12 months.

Conclusions Laparoscopic drainage of liver abscesses, in combination with systemic antibiotics, is a safe and viable alternative in all patients who require surgical drainage following failed medical or percutaneous treatment, and in those with large abscesses.

Liver abscesses, although relatively rare in the Western world^{1,2}, are commonly encountered in tropical regions. Traditionally, surgical treatment for such abscesses involved open drainage of the abscess through a hepatotomy, via a transperitoneal or retroperitoneal approach³. This provided good results in a disease that generally had a fatal outcome if left untreated⁴.

With the advent of ultrasonography and computed tomography (CT) in the 1970s, radiologically guided drainage in combination with intravenous broad-spectrum antibiotics, effective against both aerobic and anaerobic organisms, has proved to be both simple and effective⁵. However, large or multiloculated abscesses were often treated inadequately and the failure rate was high because drainage catheters were of small calibre, preventing adequate drainage of the highly viscous pus.

With increasing experience in minimal access surgery^{6–9}, the endoscopic approach is being used for more and more operations, including emergencies. Laparoscopic drainage of liver abscesses represents an attractive alternative to open surgical drainage. This paper presents the authors' experience in the treatment of 20 patients over a period of 48 months using this technique.

Patients and methods

Patient selection

Thirty-six patients suffering from hepatic abscess were managed interventionally between July 1992 and June 1996. Sixteen patients were successfully treated with percutaneous drainage and 20 were judged to require surgical drainage and selected for laparoscopic drainage of the abscess. Of the latter patients, 15 had had percutaneous drainage attempted previously. The patients were followed prospectively and factors studied included clinical presentation, investigations, surgical indications, surgical technique and outcome. Indications for surgical drainage were:

(1) failed medical treatment with antibiotics; (2) failed or contraindicated radiologically guided percutaneous drainage; and (3) abscesses larger than 6 cm with toxic symptoms such as high fever or septicaemia where urgent effective drainage was mandatory.

All patients had preoperative ultrasonographic confirmation of the abscess, and 17 also underwent CT for preoperative localization of the abscess.

Operative technique

All patients were started on intravenous antibiotics, and the laparoscopic procedure was performed under general anaesthesia with endotracheal intubation. The patient was placed in the reverse Trendelenburg position and a pneumoperitoneum was created with a Veress needle to a pressure of 9–12 mmHg.

For most abscesses three laparoscopic ports were adequate for access: a 10-mm subumbilical port, a 5- or 10-mm port in the right mid-clavicular line and another in the anterior axillary line, 2–4 cm below the costal margin. Inferiorly located abscesses required a fourth port sited to the left of the midline below the costal margin. Fan retractors were then used to lift the liver, allowing access to the abscess.

Laparoscopic localization of the liver abscess is more difficult than in open surgery, owing to the lack of tactile feedback. A combination of several methods is usually required: (1) identification of a fluctuant bulge on the surface of the liver; (2) change in colour of the liver surface from pale to brawny red superficial to the abscess; (3) the presence of fibrinous adhesions between the liver and the parietal peritoneum; and (4) aspiration with a long endoscopic aspiration or spinal needle. All abscesses were identified with the above techniques.

Pus aspirated from the abscess was sent for culture and determination of sensitivity to antibiotics. Subsequently, the point of the blunt forceps was used to follow the needle tract into the abscess. Drainage of the abscess was performed by suction with a suction irrigator. This was followed by copious irrigation of the cavity and peritoneal space with up to 6 litres of warm saline, with the last 500 ml containing 80 mg of gentamicin. In the event of bleeding, operative manoeuvres such as leaving the forceps *in situ* for about 5 min to allow the blood to clot and seal the tract, or passing the drainage tube through to the cavity which then tamponades the walls of the tract, were found to be

effective. In all patients blood loss never exceeded 250 ml as measured in the suction bottle at end of surgery. All patients had two large tube drains (chest tube size 24–28 Fr) inserted, one into the abscess cavity and another in the right or left subphrenic space adjacent to the drainage site in the liver.

After operation analgesia in the form of intramuscular pethidine was administered and patients were monitored for progression of sepsis, jaundice and bleeding. Time to oral feeding, full oral diet, ambulation and discharge from hospital was documented.

Ultrasonography or CT was performed weekly in all patients, starting 1 week following drainage. Once this confirmed solidification of the abscess cavity and resolution of symptoms of the abscess, the drainage tubes were removed and the patient was discharged from hospital.

Results

There were ten men and ten women with a mean age of 49 (range 38–68) years. The presenting symptoms were as shown in Table 1. All patients presented with fever and upper abdominal pain.

Thirteen patients had right lobe and seven had left lobe abscesses. The diameter of the abscesses ranged from 6 to 25 (mean 10.5) cm, as measured by ultrasonography and CT. Eighteen were pyogenic liver abscesses with positive pus and blood cultures for *Klebsiella* species, and there were two amoebic abscesses.

In 11 patients aetiological factors for the liver abscess could be identified (Table 2). Two patients had associated biliary tract sepsis from acute cholecystitis, and nine had poorly controlled diabetes mellitus. However, in seven patients there were no signs and symptoms to indicate the cause of the abscess.

Mean operating time was 38 (range 25–120) min. This included the two patients with acute cholecystitis who had concurrent laparoscopic cholecystectomies performed. There were no intraoperative complications.

All patients were able to drink orally by the first postoperative day and all were ambulating and on a full oral diet by the second postoperative day. No patient

required any form of pain relief after 48 h and four patients required only one dose of intramuscular pethidine after operation (Fig. 1). Fifteen of the 20 patients had resolution of fever by the second postoperative day (Fig. 2).

Initial success was found in 17 of the 20 patients. In three patients the fever recurred, indicating reaccumulation or recurrence at a different site. Of these three patients, one had a reaccumulation of the abscess 1 week following drainage at the same site as a result of a blocked drainage tube from clots. This necessitated a change of the drainage tube along the same tract allowing 400 ml of pus to drain with resolution of symptoms. Two other patients developed recurrent abscesses at different sites. One had a 3-cm abscess at a different site and was treated successfully with intravenous antibiotics for 2 weeks until complete resolution. The other patient required a second laparoscopic drainage procedure because of a large 10-cm diameter abscess which formed the other half of a dumbbell-shaped abscess. The initial

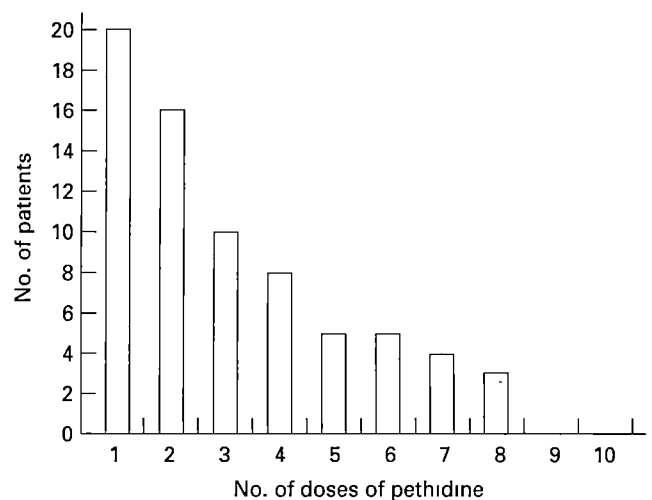


Fig. 1 Postoperative pain relief required by 20 patients. Pethidine was given intramuscularly at 6-h intervals, as required

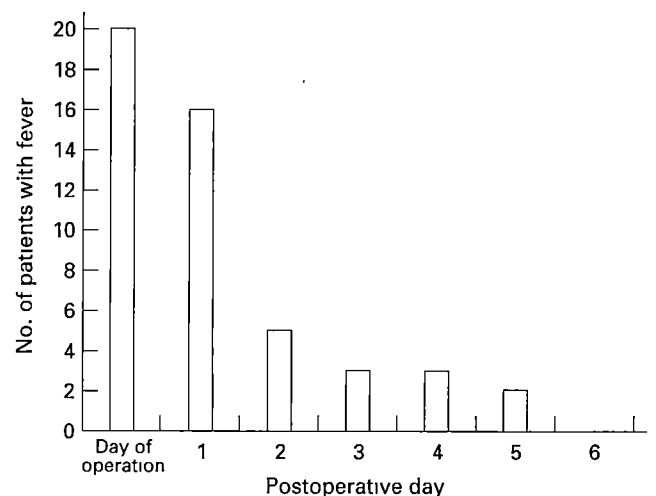


Fig. 2 Resolution of fever after operation

Table 1 Clinical features of 20 patients with liver abscess

Signs and associated illness	No. of patients
Abdominal pain	20
Fever > 38°C	20
Jaundice	8
Septicaemic shock	1
Diabetes mellitus	9

Table 2 Causes of liver abscess in 20 patients

Causative factor	Site		Total
	Right	Left	
Amoebiasis	2	0	2
Cholelithiasis	1	1	2
Diabetes mellitus	6	3	9
Cryptogenic	4	3	7

drainage tube drained one abscess cavity well but did not drain the other cavity adequately.

There was no wound infection or death, and no other surgical or medical postoperative complications were seen in the series. The mean duration of follow-up was 9 (range 5–12) months. Repeat ultrasonography or CT gave normal findings in all patients 2–4 months later.

Discussion

Historically, the diagnosis of liver abscess was associated with high morbidity and mortality rates. Often there is delay in diagnosis because the clinical picture of a hepatic abscess can be characterized by a variety of non-specific constitutional symptoms^{10–12}. With the introduction of high-resolution imaging techniques such as ultrasonography and CT, advances in bacteriology and the development of more potent antibiotics, the outcome for such patients has generally improved. Mortality rates have declined from 70 per cent in the preantibiotic era¹⁰ to between 0 and 15 per cent in the past decade^{11,13–16}.

Since the late 1970s, radiologically guided percutaneous drainage has been the mainstay for interventional management of liver abscess^{17,18}. However, the failure rate is still high (36 per cent)¹³ when compared with open surgery. Also, not all liver abscesses are amenable to percutaneous drainage. Contraindications include the presence of ascites, proximity of vital structures especially with abscesses of the left lobe, coagulation abnormalities and coexistence of an indication for laparotomy, for example acute cholangitis¹⁶. In such instances surgical drainage would be required.

With the advent and renewed popularity of laparoscopic surgery, laparoscopic drainage has presented an alternative to open surgical drainage of liver abscesses, offering the potential advantages associated with minimal access surgery. These include a decrease in the morbidity associated with a large laparotomy wound as well as the potential for faster postoperative recovery and shorter hospital stay. There are also advantages over percutaneous drainage, including the opportunity to explore the abdomen adequately and the ability to insert large-bore tube drains. The laparoscopic procedure is also potentially repeatable, as was demonstrated in the patient with the dumbbell-shaped abscess.

The results of this study compare favourably in terms of success rate and morbidity to those utilizing percutaneous drainage under image guidance as the mainstay of treatment^{3,17,19–22}. The advantage of the laparoscopic procedure was clinically obvious in the postoperative period as all the patients were comfortably free from pain, taking a full diet and ambulating actively by the second postoperative day. However, owing to the adoption of a policy of awaiting computed tomographic or ultrasonographic confirmation of resolution of the abscess cavity on the seventh postoperative day before removing the drains, the overall hospital stay was not much shorter than that for open drainage.

The findings of this study suggest that minimal access surgical drainage of liver abscesses, in combination with systemic antibiotics, is a safe and viable alternative in all patients who require open drainage following failed

medical or percutaneous treatment, or when large abscesses are present.

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Effect of endoscopic sphincterotomy and interval cholecystectomy on late outcome after gallstone pancreatitis

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Background Endoscopic sphincterotomy alone, or followed by cholecystectomy, are options in patients with gallstone pancreatitis.

Methods Ninety-six patients of median age 74 (range 30–93) years with gallstone pancreatitis had endoscopic retrograde cholangiography and were followed for a median of 84 (range 33–168) months. Forty-eight of 49 patients with, and nine of 47 without, common bile duct (CBD) stones had urgent endoscopic sphincterotomy. One patient with, and six without, CBD stones had delayed endoscopic sphincterotomy a median of 35 (range 12–111) days after acute pancreatitis. Thus, 64 patients had endoscopic sphincterotomy (group 1) and 32 did not (group 2). Fifteen and 16 patients in each group respectively had interval cholecystectomy after a median of 3 months and 1 month.

Results Patients in groups 1 and 2 had similar rates of interval cholecystectomy (15 of 64 *versus* 16 of 32 patients respectively) or required cholecystectomy (15 of 49 *versus* five of 16 patients), recurrent CBD calculi (three of 64 *versus* three of 32 patients) or total length of hospitalization after interval cholecystectomy (median 15.5 and 15 days) or required (median 22 and 24 days) cholecystectomy. The overall incidence of recurrent pancreatitis was one of 64 patients in group 1 and five of 32 in group 2 ($P = 0.02$), but after interval cholecystectomy the recurrence rate of biliopancreatic symptoms was similar (one of 15 patients *versus* three of 16 patients respectively).

Conclusion Endoscopic sphincterotomy, but not interval cholecystectomy, reduced the overall incidence of recurrent pancreatitis, but not of late biliary complications. Some 31 per cent of the patients required cholecystectomy, suggesting that routine cholecystectomy should be considered in fit patients following acute pancreatitis.

Endoscopic sphincterotomy has gained wide acceptance as a treatment for common bile duct (CBD) calculi. The procedure has low complication and mortality rates of 4.4–10.4 and 0.4–1.5 per cent, respectively^{1–3}. Presently it is used in most patients with bile duct stones and also in patients with gallstone pancreatitis^{4,5}, regardless of age. After an attack of gallstone pancreatitis, cholecystectomy is advocated. When urgent endoscopic retrograde cholangiography (ERC) does not reveal CBD calculi 'prophylactic' endoscopic sphincterotomy may^{6–8}, or may not^{5,9}, be recommended. Furthermore, endoscopic sphincterotomy alone has been proposed as an alternative to cholecystectomy^{6–8} in selected patients after gallstone pancreatitis. The main objectives of this retrospective study were to establish the need for subsequent cholecystectomy in patients who had endoscopic sphincterotomy for gallstone pancreatitis, and the incidence of recurrent pancreatitis in those who had interval cholecystectomy after the first attack. Patients with, and without, CBD stones at ERC were included in the study.

Patients and methods

Between 1981 and 1992, 417 patients with bile duct calculi were scheduled for endoscopic sphincterotomy in this department. Some 265 patients (64 per cent) had an intact gallbladder, 49 of whom had the presumptive diagnosis of gallstone pancreatitis before (one patient) or at the time of (48 patients) ERC and endoscopic sphincterotomy (48 procedures were urgent, one was elective). The criteria suggestive of the diagnosis have been

described previously^{5,8,10–12}. During the same interval, 47 patients with an intact calculous gallbladder and similar signs of pancreatitis were investigated by ERC, but no CBD calculi were found. In this group, elective ERC (20 patients) was performed 12–111 (median 35) days after gallstone pancreatitis. All 49 patients with, and 15 of the 47 patients without, CBD stones underwent endoscopic sphincterotomy (nine urgent, six elective). Patients who had endoscopic sphincterotomy ($n = 64$, group 1) had a median age of 76 (range 42–93) years. Patients with an intact papilla of Vater ($n = 32$, group 2) had a median age of 68 (range 30–89) years (Table 1). The female to male ratio was 1.9 in both groups. Median follow-up after endoscopic sphincterotomy was 79 (range 33–163) months in group 1 and 91 (range 34–168) months in group 2.

The presence of bile duct calculi was diagnosed by ERC. During cholangiography complete opacification of extrahepatic

Table 1 Impact of endoscopic sphincterotomy and subsequent interval cholecystectomy on the incidence of recurrent pancreatitis

	Endoscopic sphincterotomy		Total with recurrent pancreatitis
	Yes (group 1, $n = 64$)	No (group 2; $n = 32$)	
Interval cholecystectomy			
Yes ($n = 31$)	15 (0)	16 (3)	(3)
No ($n = 65$)	49 (1)	16 (2)	(3)
Total with recurrent pancreatitis	(1)	(5)*	

* $P = 0.02$ (group 2 *versus* group 1, Fisher's exact test)

and central intrahepatic bile ducts was achieved at deep cannulation in 98 and 100 per cent of the patients in groups 1 and 2 respectively. No additional effort was made to outline the entire gallbladder by contrast medium if this was not accomplished simultaneously with bile duct opacification. Some 75 per cent of patients had the bile ducts cleared at the first attempt using standard equipment and endoscopic techniques, including mechanical lithotripsy in recent years. When cholecystectomy was done, the bile duct was cleared surgically. Patients' hospital records and deceased patients' death certificates or post-mortem examination reports were reviewed. Surviving patients were interviewed in the outpatient clinic or by telephone.

The χ^2 test was used to analyse discrete clinical variables and Fisher's exact test was chosen when the number of observations was small. Student's *t* paired test was used for single comparison of continuous parameters. Non-gaussian distributed values were compared with the Mann-Whitney *U* test (two tailed) (QuickStat; Sapio, Lund, Sweden). *P* values are given only when differences were significant ($P < 0.05$).

Results

Forty-seven of 49 patients with bile duct stones and the gallbladder *in situ* had successful endoscopic bile duct clearance. Both patients with retained stones after endoscopic sphincterotomy had cholecystectomy with choledocholithotomy. There were two early major complications in 15 patients having elective endoscopic sphincterotomy: one case of pancreatitis and one of cholangitis¹³. Cholecystectomy was scheduled despite the absence of recurrent biliary symptoms in 15 patients in group 1 and in 16 in group 2 (Figs. 1 and 2), and was performed a median of 90 (range 4–304) days and 30 (1–259) days after endoscopic sphincterotomy respectively. Four of the 15 patients in group 1 and eight of the 16 in group 2 who had interval cholecystectomy had recurrent pancreatitis or cholecystitis–cholangitis before admission. Some 20 (31 per cent) of the 65 conservatively treated patients have required cholecystectomy. Operations were done electively in all but eight and two patients in groups 1 and 2 respectively. Recurrent bile duct calculi were detected in three (5 per cent) of the 64 patients in group 1 and in two of the 32 in group 2, at cholecystectomy for biliary colic ($n=2$; 108 and 204 days after ERC and endoscopic sphincterotomy), recurrent cholecystitis ($n=1$; after 399 days) or recurrent pancreatitis ($n=1$; after 19 days), or at repeated ERC

No endoscopic sphincterotomy (group 2)

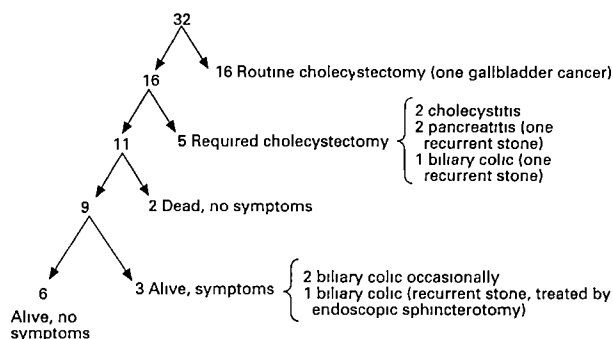


Fig. 2 Outcome in 32 patients with an intact papilla of Vater (group 2)

with endoscopic sphincterotomy for pain and jaundice ($n=1$; 52 months after the first ERC). One patient in group 1 had successful endoscopic treatment of recurrent CBD stones 5 months after cholecystectomy.

Total length of hospital stay (hospitalization at initial admission for pancreatitis plus subsequent cholecystectomy) in groups 1 and 2 was similar between patients who had interval cholecystectomy (median 15.5 (range 8–59) and 15 (range 8–114) days respectively) or who subsequently required cholecystectomy (median 22 (range 11–49) and 24 (range 5–37) days respectively). There were no differences in the rate of operative morbidity (five of 31 and four of 20 respectively). There was one death in group 2 as a result of late complications 3 months after a peroperative bile duct injury at interval cholecystectomy.

After initial endoscopic sphincterotomy alone, 18 and 19 of the 20 required cholecystectomies were performed within 12 and 24 months respectively. None was necessary beyond 3 years of follow-up. During follow-up, one of the 15 patients in group 1 who had interval cholecystectomy experienced recurrent symptoms (cholangitis), compared with three of the 16 in group 2 (all recurrent pancreatitis, one patient twice). Eight of the 16 patients initially treated conservatively in group 2 had recurrent biliary symptoms; eight remained asymptomatic. Five of 31 patients who had interval cholecystectomy died from unassociated disease during follow-up, compared with 29 (45 per cent) of 65 conservatively treated patients ($P=0.01$, χ^2 test). No difference in mortality rate was noted, however, between patients initially treated conservatively and who subsequently required cholecystectomy (eight of 20 died) and those who did not need cholecystectomy (20 of 45 died). One patient who had interval cholecystectomy 7 days after endoscopic sphincterotomy and one who had surgery for acute cholecystitis 6 months after sphincterotomy were found to have advanced gallbladder carcinoma. They died 15 and 4 months respectively after operation. A further patient in group 2 had interval cholecystectomy 19 days after ERC and was found to have a non-invasive carcinoma of the gallbladder, but died from recurrent cancer 55 months later.

Among the conservatively treated patients, 49 of the ERC films were retrieved and reviewed. The incidence of blocked cystic duct was similar whether or not endoscopic sphincterotomy was performed (eight of 34 patients

Endoscopic sphincterotomy (group 1)

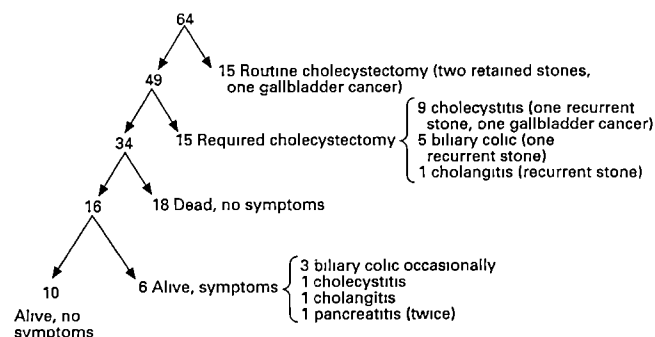


Fig. 1 Outcome in 64 patients who had endoscopic sphincterotomy (group 1)

compared with four of 15) and was not related to age (three of 23 aged less than 74 *versus* nine of 42 aged over 74 years). Among patients with complete opacification ($n=29$) and no or partial opacification ($n=20$) of the gallbladder at ERC, ten and six respectively required cholecystectomy.

Discussion

All patients in this study had pancreatitis despite the absence of CBD stones at ERC in 47 of the patients (27 of whom were treated urgently). Pancreatitis was distinguished from hyperamylasaemia using recognized, clinical features and biochemical factors^{11,14-18}. In this (64 per cent, 48 of 75) and other studies (about 70 per cent)^{19,20} the majority of patients with the presumptive diagnosis of acute gallstone pancreatitis have been found to retain CBD stones or to have evidence of recent passage.

Cholecystectomy has been advocated after gallstone pancreatitis because of the high incidence (about 30 per cent) of recurrent pancreatitis²¹⁻²⁴. In elderly patients, however, with concomitant bile duct stones successfully removed endoscopically, cholecystectomy may not be necessary⁶⁻⁸. In 31 patients interval cholecystectomy was preferred to conservative management, and the operations were performed a median of 3 months after ERC with endoscopic sphincterotomy. The presence and severity of concomitant diseases influenced selection for interval cholecystectomy, as witness by the high mortality rate in patients selected for conservative treatment.

The decision to perform cholecystectomy is affected by knowledge about the rate of recurrence of biliary colic, bile duct stones, acute pancreatitis, acute cholecystitis and late complications of endoscopic sphincterotomy. When biliary colic recurs, cholecystectomy should be considered. Twelve (18 per cent) of 65 patients treated conservatively subsequently experienced biliary colic and six required cholecystectomy, similar to previous reports^{25,26}.

Recurrent bile duct calculi have been reported in 2-6 per cent^{25,27,28} of patients after endoscopic sphincterotomy, compared with 5 per cent (three of 64) in this study. Low rates (4-8 per cent) of recurrent pancreatitis after surgery for gallstone pancreatitis have been noted during long-term follow-up²⁹⁻³¹. The present findings are inconsistent, as three of 16 patients in group 2 who had interval cholecystectomy developed recurrent pancreatitis. Liver function test results were within the reference range in all these patients, suggesting that this was not biliary pancreatitis. Moreover, two of five required cholecystectomies in group 2 were performed because of recurrent pancreatitis. In contrast, four conservatively treated patients in group 2 developed recurrent stones ($n=2$), recurrent pancreatitis ($n=1$) or both ($n=1$), as did three of the patients who had interval cholecystectomy. However, three patients developed recurrent calculi and one had recurrent pancreatitis in group 1, although the overall incidence of recurrent pancreatitis was significantly ($P=0.02$) lower in this group (Table 1). As the pancreatitis attacks were not necessarily of biliary origin in three patients from group 2, it is unlikely that endoscopic sphincterotomy could have prevented recurrent symptoms. Endoscopic sphincterotomy might have reduced the need for subsequent cholecystectomy in three of five patients in group 2. Contradicting these findings and favouring routine endoscopic sphincterotomy, Kelly

and Swaney³² reported recurrent pancreatitis in 92 per cent of patients with retained or recurrent CBD stones even after cholecystectomy. The corresponding incidence was one of six patients in the present study, and 12 per cent in patients with an intact gallbladder and recurrent stones in a previous study from the authors' department²⁷. Thus, the results of this study do not favour routine endoscopic sphincterotomy in patients with gallstone pancreatitis but no demonstrable CBD stones.

Previous investigations of endoscopic sphincterotomy in patients with CBD stones and an intact gallbladder showed that 67-98 per cent of patients did not require cholecystectomy and that 70-96 per cent of patients were symptom-free or improved^{25,27,28}. The corresponding values in this study were 69 per cent (34 of 49) and 63 per cent (31 of 49) respectively (Fig. 1), suggesting that patients with gallstone pancreatitis are at greater risk of late biliopancreatic complications. Emergency cholecystectomy is reported to be required in 4-6 per cent of patients after endoscopic sphincterotomy^{25,33,34}, compared with 15 per cent (10 of 65) in the present study, owing to the increased risk of acute cholecystitis after endoscopic sphincterotomy for gallstone pancreatitis³⁵. As the overall rate of cholecystectomy in this study was high (31 per cent in both groups), cholecystectomy should be considered in fit patients following gallstone pancreatitis.

In a previous study²⁷ from this department, patients with complete opacification of the gallbladder at ERC were significantly more likely to develop cholecystitis or biliary colic requiring cholecystectomy. No such difference was observed in the present study, suggesting another mechanism in patients with the small (less than 3 mm) gallbladder stones associated with gallstone pancreatitis.

In this long-term study (median follow-up 84 months) of patients with pancreatitis, the incidence of recurrent biliary complications was not affected by whether or not endoscopic sphincterotomy was done after the initial attack. Late symptoms were, however, common (21 of 49 patients after endoscopic sphincterotomy and eight of 16 after no endoscopic sphincterotomy) and cholecystectomy was required in 31 per cent of patients treated conservatively. Endoscopic sphincterotomy significantly reduced the incidence of recurrent pancreatitis, independent of whether the gallbladder was removed. These results support a management plan that includes routine cholecystectomy in fit patients after endoscopic treatment of gallstone pancreatitis. Endoscopic sphincterotomy, however, is not justified if CBD calculi are not identified.

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Genetic alterations in chronic pancreatitis: evidence for early occurrence of *p53* but not *K-ras* mutations

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Background In patients suffering from chronic pancreatitis the risk for the development of pancreatic cancer ranges from 4 to 6 per cent. Various mutations are associated with pancreatic cancer, especially of *p53* and *K-ras*. The incidence of these mutations in resected chronic pancreatic tissue was investigated.

Methods In the present study DNA from 80 samples of tissue from patients with chronic pancreatitis was isolated and subjected to single-strand conformation polymorphism (SSCP) analysis of *p53* exons 5–9 and restriction fragment length polymorphism analysis of *K-ras* (codon 12).

Results No mutations in the *K-ras* gene were detected. On SSCP analysis, eight of 80 cases of chronic pancreatitis showed alterations (two in exon 5, four in exon 6, two in exon 7). DNA sequence analysis revealed one deletion of 21 amino acids (exon 5), four polymorphisms in exon 6 with no change in the amino acid sequence, one point mutation in exon 5, and two point mutations located in the intron between exons 6 and 7.

Conclusion These data show that in some cases of chronic pancreatitis mutations in the *p53* gene occur without morphological evidence of pancreatic cancer

Despite improved diagnostic and therapeutic facilities, cancer of the pancreas still has a poor prognosis¹. At time of admission to the hospital only one-third of tumours are resectable, and even in patients undergoing resection of the tumour, median survival is seldom longer than 2 years². Although no specific reasons for the development of pancreatic cancer are known, several factors such as alcohol, smoking and nitrosamines are thought to increase the risk^{3–5}. Besides these risk factors, several reports have provided evidence that chronic pancreatitis is associated with an increased risk of pancreatic cancer^{6–8}. Analysis of 395 patients who underwent surgery in this institution for chronic pancreatitis revealed that the frequency of pancreatic cancer in patients with pre-existing chronic pancreatitis was 3.8 per cent, which is significantly higher than that in the general population⁸.

Chronic pancreatitis and pancreatic carcinoma have been studied extensively at subcellular and molecular levels (for review see reference 9). Although many alterations in messenger RNA (mRNA) expression were found in chronic pancreatitis compared with normal pancreatic tissue, only a few studies have reported molecular alterations at the DNA level. *K-ras* mutations, which occur in 75–95 per cent of pancreatic cancers¹⁰, were not found in chronic pancreatitis, although they are thought to occur very early in tumorigenesis¹¹. A review of the literature revealed that of 110 cases of chronic pancreatitis that were tested for *K-ras* mutations only one exhibited a *K-ras* mutation^{12–17}, whereas *K-ras* mutations were frequent in mucous cell hyperplasia^{18–20} (Table 1). Mutations in the *p53* gene occur in almost 50 per cent of pancreatic carcinomas^{21,22}. However, only one report exists which investigated six cases of chronic pancreatitis for *p53* mutations at the DNA level. In this study no *p53*

mutations were found in six cases of chronic pancreatitis²¹. In pancreatic cancer, mutations in the *p53* gene seem to be more frequent in advanced tumour stages and appear to be associated with a poorer prognosis than pancreatic tumours bearing wild-type *p53*²³.

The aim of this study was to determine whether mutations in the *p53* or *K-ras* gene occur in chronic pancreatitis, which could serve as a possible screening method for high-risk cases of chronic pancreatitis.

Patients and methods

Patients

DNA was isolated from 80 samples of tissue from patients with chronic pancreatitis undergoing duodenum-preserving pancreatic head resection between February 1994 and August 1995.

Table 1 Previous studies of *K-ras* mutations in chronic pancreatitis and mucous cell hyperplasia

Reference	Year	Mutated	Not mutated	Comments
Tada <i>et al.</i> ¹²	1991	0	6	CP, tissue
Yanagisawa <i>et al.</i> ¹⁹	1993	10	6	Mucous cell hyperplasia
Watanabe <i>et al.</i> ¹⁴	1993	0	18	CP, pancreatic juice
Kondo <i>et al.</i> ¹⁶	1994	0	10	CP, pancreatic juice
Van Laethem <i>et al.</i> ¹⁵	1995	0	16	CP, pancreatic duct brushes
Iguchi <i>et al.</i> ¹⁷	1996	1	40	CP, duodenal juice
Tada <i>et al.</i> ¹⁸	1996	12	26	Hyperplastic ducts, no cancer, no chronic pancreatitis
Watanabe <i>et al.</i> ¹³	1996	0	20	CP, duodenal juice

CP, chronic pancreatitis

Immediately after resection a random sample of tissue was snap-frozen in liquid nitrogen and stored at -80°C until DNA was isolated. The median age was 44 (range 27–73) years, 64 patients were men. No patient died in the perioperative or postoperative period.

The diagnosis of chronic pancreatitis was confirmed by a pathologist. DNA was isolated from one random sample. Before DNA isolation, chronic pancreatitis was assessed by haematoxylin staining of the tissue block. Only tissue samples that contained areas of chronic pancreatitis exceeding 80 per cent were included in the analysis.

Detection of p53 mutation

Single-strand conformation polymorphism (SSCP) analysis was performed as described previously²⁴. In brief, polymerase chain reaction (PCR) conditions were as follows: in a total volume of 25 μl , 500 ng of genomic DNA was incubated in Tris-hydrochloric acid 10 mmol/l (pH 8.3), magnesium chloride 2 mmol/l, potassium chloride 50 mmol/l, 0.01 per cent gelatin, deoxynucleotide triphosphates 100 mmol/l, 1 $\mu\text{mol/l}$ of each primer, 5 μCi of $\alpha^{32}\text{P}$ deoxycytosine triphosphate and 1 unit of Taq polymerase from *Thermus Aquaticus* DNA polymerase (Perkin Elmer, Branchburg, New Jersey, USA). Amplifications were performed for 35 cycles consisting of 30 s at 94°C , 30 s at 50 – 65°C depending on the primer, and 45 s at 72°C . SSCP was performed using MDE gels (long ranger gel solution; Boehringer Ingelheim, Heidelberg, Germany) followed by 12 h exposure to X-ray films. Sequencing was performed using an automated sequencing system (ALF; Pharmacia, Freiburg, Germany).

Detection of K-ras mutations

Restriction fragment length polymorphism (RFLP) analysis was carried out as described previously²⁵. In brief, approximately 1 μg of DNA was amplified using 100 ng each of primers K-ras 12-13-5'-BstNI and 12-13-3'-WT in a volume of 100 μl . After 15 cycles, 20 μl of the PCR product was digested with 20 units of BstNI enzyme at 60°C for 3 h, and 10 μl of the digest was used as template for a second round of PCR with 150 ng each of primers K-ras 12-13-3'-BstNI and 12-13-5'-BstNI in a volume of 100 μl . The entire PCR product was digested for 2 h, precipitated and separated on a 2 per cent agarose gel.

Results

Although this RFLP method can detect one K-ras mutation in 1000 wild-type K-ras templates, no mutations were found in all specimens of chronic pancreatitis (Table 2). As positive control samples, DNA was isolated from pancreatic carcinoma tissue and screened for K-ras mutations. Using this assay, K-ras mutations at codon 12

could be detected in 75 per cent of pancreatic cancer tissues (data not shown). Surprisingly, SSCP analysis of exons 5–9 revealed alterations in eight (10 per cent) of the patients investigated (Table 2; Fig. 1).

Two cases showed alterations in exon 5, four alterations were found in exon 6, and two in exon 7. These alterations were found in different cases.

Sequencing of the eight samples of DNA that had shown alteration in SSCP analysis of p53 revealed that all cases with alterations in exon 6 showed a CGA→CGG transition at codon 213 without causing a change in the amino acid sequence (both CGA and CGG code for arginine). One case with alterations in exon 5 showed a GGC→GAC point mutation at codon 154, causing replacement of glycine by asparagine. The other alteration in exon 5 was a frameshift mutation leading to the deletion of 21 nucleotides. The two cases with alterations in exon 7 both showed a G→C transversion located in the intron between exons 6 and 7 at position 25 (Table 3). The

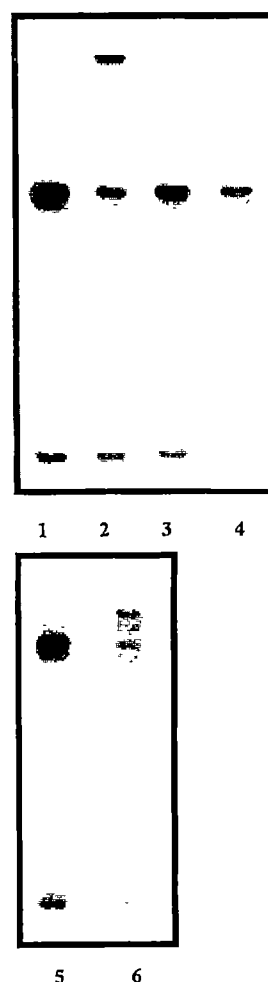


Fig. 1 Single-strand conformation polymorphism gels (exon 5) of six cases of chronic pancreatitis including the two alterations of the p53 gene in chronic pancreatitis which led to an altered amino acid sequence. Both mutations were located in exon 5. Lanes 1, 3, 4 and 5 show the typical bands for wild-type p53, whereas the electrophoretic mobility of the polymerase chain reaction (PCR) products in lanes 2 and 6 are suspect for mutation. Sequencing of the PCR products revealed a deletion of 21 nucleotides (lane 2) and an exchange of GGC to GAC at codon 154 (lane 6).

Table 2 Alterations in p53 single-strand conformation polymorphism and K-ras restriction fragment length polymorphism

	SSCP of p53					RFLP of K-ras codon 12
	Exon 5	Exon 6	Exon 7	Exon 8	Exon 9	
Alterations (n = 80)	2	4	2	0	0	0

SSCP, single-strand conformation polymorphism; RFLP, restriction fragment length polymorphism

Table 3 Analysis of alterations in *p53* by sequencing

No. of cases	Exon	Mutation	Type of mutation	Consequence
4	6	CGA→CGG	Point mutation	None, polymorphism
1	5	—	Deletion	Deletion of 21 nucleotides
1	5	GGC→GAC	Point mutation	Glycine→asparagine
2	6–7	G→C	Point mutation	None, polymorphism?

polymorphism in exon 6 has also been described in a series of patients with atherosclerotic lesions²⁶.

Discussion

The development of pancreatic cancer during chronic pancreatitis is still controversial, partly because of the limited number of cases. In a prospective trial, 245 patients with chronic pancreatitis were observed for 10.4 years. Pancreatic carcinoma was diagnosed in seven cases during that period⁶. Löwenfels and co-workers⁷ studied a population of 2015 patients retrospectively. During the observation period of 7.6 years, 56 patients developed pancreatic cancer. Molecular analysis of mRNA revealed increased expression of growth factors such as transforming growth factor α , fibroblast growth factor (FGF) α and FGF- β , as well as the epidermal growth factor receptor and *c-erbB2* in human pancreatic tissue of patients with chronic pancreatitis^{27,28}. The expression of extracellular matrix molecules and their receptors was also altered slightly in chronic pancreatitis compared with normal pancreas²⁹. These reports suggest dysregulation of a number of genes resulting in altered mRNA levels in chronic pancreatitis. Some of these changes, especially the overexpression of growth factors and their receptors, might contribute to ductal cell hyperplasia and pseudoductal cell formation.

The hypothesis of a sequential development of pancreatic cancer is supported by the observation that dysplastic structures are found frequently in specimens of chronic pancreatitis³⁰. A hyperplasia–dysplasia–carcinoma sequence seems to be more likely than a one-step process. It is now generally accepted that carcinogenesis is a multistep process³¹. Such a sequence of genetic events was first demonstrated for colonic cancer. The accumulation of genetic alterations of oncogenes and tumour suppressor genes, including activation of the *K-ras* proto-oncogene and inactivation of the *APC*, *DCC* and *p53* tumour suppressor genes, is the genetic basis for the adenoma–carcinoma sequence³¹. Mutations in the *K-ras* gene on chromosome 12p are rare in small adenomas but are found in almost 50 per cent of adenomas larger than 1 cm in diameter³², whereas inactivation of the *p53* tumour suppressor gene on chromosome 17p occurs preferentially in large adenomas and in carcinomas, typically at a later stage of the neoplastic process. In the adenoma–carcinoma sequence, *K-ras* mutations always precede *p53* inactivation^{31,32}. On the other hand, *p53* mutations seem to be early genetic events in dysplastic lesions. Patients with ulcerative colitis first develop *p53* mutations and loss of heterozygosity without evidence of *K-ras* mutation. Furthermore, *p53* mutations have been found in benign or precancerous lesions in other human tissues such as hyperplastic prostatic epithelium³³, papillomatous hyperplasia and fibroadenoma of the

breast³⁴, suggesting that *p53* mutations can also occur at a very early stage of tumorigenesis in other tissues.

No *K-ras* mutations were detected in codon 12 in chronic pancreatitis, although the RFLP method used is extremely sensitive. Interestingly, alterations were found in the *p53* gene in 10 per cent of cases. Four of the eight cases showed single base changes at the third position of a codon, not altering the amino acid sequence. The significance of this genetic polymorphism is not clear; however, it is interesting that in the multitude of reports only two studies were found that described this polymorphism^{26,35}. The alterations in two mutations clearly changed the structure of the *p53* protein by alteration of the amino acid sequence. However, it is not known whether these changes also led to an altered function or a loss of function in the *p53* gene product. With regard to the frequency of *K-ras* mutations in chronic pancreatitis, these data are consistent with previous studies that investigated pancreatic or duodenal juice (Table 1)^{13–17}. Even in pancreatic juice, where cells from all parts of the ductular system are sampled only one of 104 published cases revealed a *K-ras* mutation at codon 12^{13–17}.

These data show that in some cases of chronic pancreatitis mutations in the *p53* gene occur without morphological evidence of pancreatic cancer which could point to precancerous lesions. As the amino acid sequence was altered in only two of 80 cases of identified mutation this study will be continued to confirm the data in a larger series of patients with chronic pancreatitis.

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Structured data collection improves the diagnosis of acute appendicitis

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Background Structured preoperative data collection and computer-assisted methods are claimed to improve diagnostic accuracy in patients with acute abdominal pain. The aim of this study was to evaluate a possible age- and sex-related effect of using structured data collection in the preoperative diagnosis of patients with suspected acute appendicitis.

Methods Between 1989 and 1994, clinical and demographic data from 1764 consecutive patients were recorded. In 1990 and 1992, various detailed symptom, clinical and laboratory data were collected prospectively on a structured registration form. Age- and sex-specific diagnostic accuracy as well as perforation rate were calculated for each year.

Results Diagnostic accuracy increased significantly by 5 (95 per cent confidence interval (c.i.) 1–9) per cent when structured data registration was applied. In female patients aged between 13 and 40 years, diagnostic accuracy increased by 16 (95 per cent c.i. 8–24) per cent. Significant changes in diagnostic accuracy were not seen in other subgroups. Perforation rates remained unchanged during the entire study period.

Conclusion In this population-based study, diagnostic accuracy in patients operated on for suspected acute appendicitis increased for all patients when structured preoperative data collection was used. However, the only subgroup with a significant increase in diagnostic accuracy was female patients aged between 13 and 40 years. Perforation rate was unaffected by structured data collection.

Acute appendicitis is one of the most frequent reasons for acute abdominal operation^{1,2}. Correct preoperative diagnosis can sometimes be difficult^{3,4}. Computer-assisted diagnosis^{5,6} or the use of structured data collection sheets^{7,8} in this group of patients has been reported to reduce the number of unnecessary appendicectomies. However, these methods have not been used routinely in clinical practice⁹. While computer-based systems are regarded as expensive and impractical, structured data collection forms can be used easily in a clinical setting. The effect of a structured data collection form on the diagnostic accuracy of acute appendicitis was studied in 1764 consecutive patients with respect to various age groups and sex.

Patients and methods

Patients

The authors' department is the only one providing an emergency service for a population of 265 000 people in an urban and rural catchment area. Between 1989 and 1994, 1764 patients (943 (53 per cent) male and 821 (47 per cent) female patients) underwent operation for suspected acute appendicitis.

Data registration

All appendicectomies were registered consecutively. Incidental appendicectomies were not included. All specimens were examined microscopically. The final diagnosis of acute appendicitis was based on histological findings.

Patients admitted for suspected acute appendicitis were examined initially by junior staff with varying experience. The final decision with regard to operation was made by either a senior registrar or consultant surgeon. Staff members involved in the diagnostic investigation of patients with suspected acute appendicitis changed during the study period, on average 18 different doctors at any given time.

During 1990 and 1992, detailed symptom, clinical and laboratory variables were recorded prospectively to evaluate

possible diagnostic features of acute appendicitis. Data were recorded using a structured registration form (see Appendix). The likelihood of the patient having acute appendicitis was considered and recorded before operation by the surgeon responsible.

Definitions

Diagnostic accuracy was defined as the proportion of removed appendices with histologically proven acute appendicitis of the total number of laparotomies for suspected acute appendicitis. Perforation rate was defined as proportion of perforated appendices in patients with histologically proven acute appendicitis.

Statistical analysis

The effect of using the structured data form was assessed by calculating and comparing diagnostic accuracy for various years with and without structured data collection. The difference in diagnostic accuracy between various years was calculated, as well as the 95 per cent confidence interval (c.i.) for the difference of proportions¹⁰. A confidence interval different from zero was considered statistically significant¹¹. Age-specific analysis was performed for five clinically relevant age groups: small children (0–4 years), children (5–12 years), adolescents and young adults (13–40 years), adults (41–65 years) and elderly (greater than 65 years).

The χ^2 test was used for categorical data. $P < 0.05$ was considered statistically significant.

Results

The distributions of age and sex are shown in Fig. 1. The male:female ratio was 1.15:1. Among small children and the elderly, significantly more female patients were encountered ($\chi^2 = 13.6$, 4 d. f., $P = 0.009$). The age and sex distributions were constant during the study period.

Diagnostic accuracy and structured data collection

The overall diagnostic accuracy was 76 per cent. In 544 patients (31 per cent; years 1990 and 1992), the structured

Registration form was used (see Appendix). Distribution of age and sex in this group compared with that in the remaining 1220 patients was similar. Diagnostic accuracy increased from 75 to 80 per cent (5 per cent difference; 95 per cent c.i. 1–9 per cent) when structured data collection was used.

Time course of diagnostic accuracy

The overall diagnostic accuracy varied during the study period (Fig. 2). From 1989 (baseline period) to 1990 (first period with structured data collection), diagnostic accuracy increased significantly from 69 to 78 per cent (9 per cent difference; 95 per cent c.i. 2–16 per cent). The following year (1991; routine preoperative examination), diagnostic accuracy decreased slightly to 76 per cent. A significant increase in diagnostic accuracy to 83 per cent (7 per cent difference; 95 per cent c.i. 0.3–13.7 per cent) was observed after the second period (1992) of structured registration. No significant changes were observed during the last 2 years (1993 and 1994) of the study period. In 1994, diagnostic accuracy was significantly higher

compared with the baseline period, 79 versus 69 per cent (10 per cent difference; 95 per cent c.i. 3–17 per cent).

Diagnostic age and sex

Age- and sex-specific changes in diagnostic accuracy are shown in Table 1. In female patients of all age groups, diagnostic accuracy increased from 65 to 77 per cent (12 per cent difference; 95 per cent c.i. 6–18 per cent). Diagnostic accuracy remained unchanged (82 per cent) in male patients. Age-specific analysis showed that female patients between 13 and 40 years of age were the only subgroup to show significant changes when a structured registration form was used.

The changes in diagnostic accuracy in female patients during the study period are shown in Fig. 3. Diagnostic accuracy increased significantly from 1989 (56 per cent; without structured registration form) to 1990 (78 per cent; with structured registration form) (22 per cent difference; 95 per cent c.i. 12–32 per cent) and then decreased significantly to 66 per cent (12 per cent difference; 95 per cent c.i. 1.5–22 per cent) the next year. During the second period with the structured registration form (1992), an

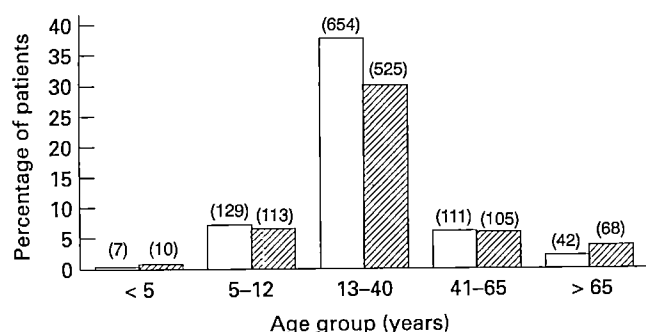


Fig. 1 Age and sex distribution of 1764 patients operated on the suspected acute appendicitis between 1989 and 1994. □, Male patients ($n = 943$; 53 per cent); ▨, female patients ($n = 821$; 47 per cent). The number of patients in the various subgroups are indicated above the bars

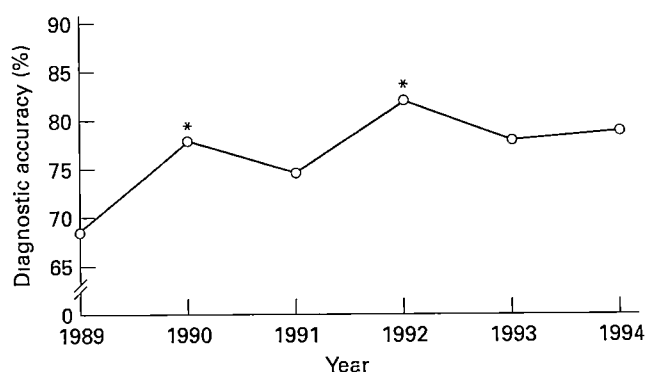


Fig. 2 Changes in diagnostic accuracy during the study period. In the years 1990 and 1992, structured data collection was used.

*Significant changes in diagnostic accuracy

Table 1 Age- and sex-related changes in diagnostic accuracy for patients without and with structured data collection

Age group (years)	Without structured data sheet		With structured data sheet		Difference in diagnostic accuracy†
	Diagnostic accuracy (%)	No. of patients*	Diagnostic accuracy (%)	No. of patients*	
Female patients					
0-4	50	6 (1)	70	4 (2)	20 (- 29 to 69)
5-12	73	79 (14)	82	34 (14)	9 (- 7 to 25)
13-40	62	369 (64)	78	156 (64)	16 (8 to 24)
41-65	78	79 (14)	73	26 (11)	- 5 (- 24 to 14)
> 65	56	44 (8)	67	24 (10)	11 (- 13 to 33)
Total		577 (100)		244 (100)	
Male patients					
0-4	50	4 (1)	33	3 (1)	- 17 (- 89 to 55)
5-12	80	91 (14)	71	38 (13)	- 9 (- 25 to 7)
13-40	84	446 (69)	83	208 (69)	- 1 (- 5 to 7)
41-65	92	75 (12)	94	36 (12)	2 (- 8 to 11)
> 65	70	27 (4)	73	15 (5)	3 (- 29 to 35)
Total		643 (100)		300 (100)	

*Values in parentheses are the percentage of patients in each subgroup by mode of data collection; †values in parentheses are 95 per cent confidence interval of the difference (positive values denote an improvement in diagnostic accuracy and negative values denote a decrease)

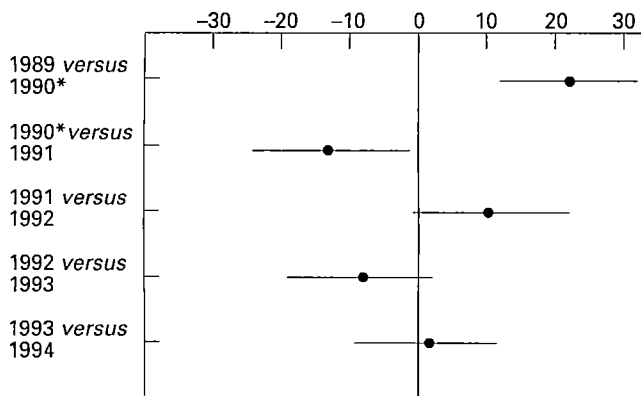


Fig. 3 Changes in diagnostic accuracy in female patients during the study period. *Differences in diagnostic accuracy between the respective years are indicated by points with 95 per cent confidence interval bars

increase was again achieved, to 77 per cent. However, this improvement was not statistically significant (11 per cent difference; 95 per cent c.i. -0.1 – 22.1 per cent). Only minor changes occurred later.

Perforation rate and structured data collection

An overall perforation rate of 21 per cent was observed during the study period. No difference was found between male (20 per cent) and female (21 per cent) patients. Between various age groups, however, there were significant differences (small children and elderly 50 and 46 per cent respectively *versus* 22 per cent in the other age groups; $\chi^2 = 27.03$, 4 d.f., $P = 0.0001$). The perforation rate was similar in periods with and without structured registration (20 per cent *versus* 21 per cent). The perforation rate with respect to various age groups and sex remained unchanged whether structured data forms were used or not

Discussion

The data from this study are based on 1764 consecutive patients from a Scandinavian population of 265 000 inhabitants. The authors' hospital is the only one providing emergency surgery for that area. Diagnostic accuracy increased significantly when a structured data registration form was used (Fig. 2). This observation agrees with that of others⁹. Several explanations have been discussed¹²: a placebo effect resulting from study conditions ('Hawthorn effect'), a checklist effect due to structured history taking and physical examination, and the effect that such a form may have on the enthusiasm of clinicians. A structured data sheet may provide a more consistent preoperative patient assessment in terms of terminology and completeness of relevant items.

Age- and sex-specific analysis showed that the only significant improvement in diagnostic accuracy during the use of a structured registration form was achieved in the subgroup of women aged between 13 and 40 years (i.e. fertile women), which is known for its low diagnostic accuracy^{3,4,13–15}. Changes in diagnostic accuracy were observed in other patient groups, but were not statistically significant. To the authors' knowledge, there are no other comparable age- and sex-specific studies on the effect of structured data collection or computer-assisted methods on diagnostic accuracy in acute appendicitis. The importance of this subgroup, representing about one-third

of all patients, is also reflected by the significant increase in diagnostic accuracy in the total study population. Traditionally, surgeons may have a more liberal attitude towards laparotomy in young female patients because of the increased risk of infertility following perforated appendicitis^{16,17}. In addition to a larger number of differential diagnoses than in male patients, this probably contributes to a higher number of unnecessary appendicectomies. Use of structured data collection and clinical assessment probably enabled improved selection for appendicectomy. Observed improvements in other age groups of female patients were not statistically significant, most likely because of small numbers.

Others² have suggested that a further increase in diagnostic accuracy is not possible either from the history and physical findings or by other means, such as computer diagnosis. Recently, various examination tools including ultrasonography¹⁵ and computer-assisted diagnosis¹⁸ or scoring systems^{19,20} have been employed to improve diagnostic accuracy. Ultrasonography is regarded as resource consuming and therefore not usable as a general diagnostic tool in all patients. Computer-assisted diagnosis has been shown to increase diagnostic accuracy^{5,6,9,19}, whereas others have reported less convincing results^{1,2,21}. Therefore, this has not become a widespread tool^{9,21,22}. The use of several diagnostic scores did not achieve clinically acceptable results²³. Laparoscopy has recently gained more attention as both the diagnostic properties and therapeutic possibilities are promising^{24,25}. However, laparoscopy is an invasive procedure performed under general anaesthesia and, with regard to feasibility and cost utility, its place still remains to be shown in patients with suspected appendicitis.

The role of a structured registration form has been emphasized by several authors as the basis of a scoring system, computer-based technique or prospective clinical trial^{9,20,24}. It is difficult to assess the degree to which a registration sheet improves selection for operation. In large surgical units where surgeons with varying clinical experience care for patients with suspected acute appendicitis, this method may enable a more consistent and complete clinical assessment. Junior staff, in particular, may benefit from the use of structured data forms by adopting a more systematic approach to patient assessment. There is some evidence of a 'carry over' effect after this technique was used in the authors' department (Fig. 2), so structured data collection may have led to improved history taking and decision-making behaviour among hospital staff.

It is concluded that the use of structured data forms improves the preoperative diagnosis of acute appendicitis significantly in a subgroup of patients in whom the diagnosis is known to be difficult (female patients aged between 13 and 40 years). Further efforts are needed to improve the clinical diagnosis in this group of patients with suspected acute appendicitis because of the unacceptably low diagnostic accuracy. The implementation of structured data forms is simple, and probably cost effective for the hospital. More importantly, individual patients may benefit significantly from improved diagnostic accuracy of this common emergency abdominal condition.

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Appendix

Structured registration form used in 1990 and 1992

Patient identification	Sex (0 = female, 1 = male)	
History		
Previous laparotomy?	0 = no, 1 = yes	
Previous periods of right iliac fossa pain	0 = no, 1 = yes	
Other relevant ongoing disease?		
First-degree relatives with earlier appendectomy?	0 = no, 1 = yes	
Clinical assessment		
Initial examination on admission		
Date/time/surgeon		
Duration of symptoms (h)		
Repeated examination, when patient observed in hospital		
Date/time/surgeon		
Duration of symptoms (h)		
Symptoms and signs	Examination 1*	Examination 2†
Classical history (pain → nausea → anorexia)	0 = no, 1 = yes	0 = no, 1 = yes
Pain shift to right iliac fossa	0 = no, 1 = yes	0 = no, 1 = yes
Worsening of pain by moving or cough	0 = no, 1 = yes	0 = no, 1 = yes
Facial rubor	0 = no, 1 = yes	0 = no, 1 = yes
Maximal tenderness over McBurney's point	0 = no, 1 = yes	0 = no, 1 = yes
Rebound tenderness over McBurney's point	0 = no, 1 = yes	0 = no, 1 = yes
Muscle guarding over McBurney's point	0 = no, 1 = yes	0 = no, 1 = yes
Rectal examination, right pelvic tenderness	0 = no, 1 = yes	0 = no, 1 = yes
Last menstruation (first day)		
Temperature	Examination 1* (°C)	Examination 2† (°C)
Urinalysis		
Glucosuria	0 = no, 1 = yes	0 = no, 1 = yes
Pyuria	0 = no, 1 = yes	0 = no, 1 = yes
Haematuria	0 = no, 1 = yes	0 = no, 1 = yes
Blood tests		
Haemoglobin	mmol/l	mmol/l
White blood count	× 10 ⁹ /l	× 10 ⁹ /l
Neutrophile granulocytes	%	%
C-reactive protein	units/l	units/l
Indication for surgery		
Clear indication to operate	0 = no, 1 = yes	0 = no, 1 = yes
Uncertain indication to operate	0 = no, 1 = yes	0 = no, 1 = yes
Operation		
Date/time/surgeon		
Peroperative diagnosis	Normal appendix Phlegmonous appendicitis Gangrenous appendicitis Perforation, local abscess Perforation, diffuse peritonitis Mesenteric lymphadenitis Gynaecological disease Other condition	
Surgical procedure(s)		
Histological diagnosis and discharge diagnosis (ICD-9)		

*On admittance to hospital; †after a variable period of observation in hospital ICD, International Classification of Diseases, 9th revision

Short note

How to secure the cystic duct at laparoscopic cholecystectomy

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Leakage of bile from the cystic duct is a recognized complication of laparoscopic cholecystectomy¹, thought to be related to technical factors at the time of operation or to failure of the occlusive mechanism in the early postoperative period. Methods of securing the cystic duct include clip ligation with metallic or absorbable clips and occlusion by a ligature. The relative merits of these techniques remain unclear, however, and the factors related to their failure are incompletely understood.

Materials and methods

Freshly removed human gallbladders with an intact length of cystic duct were studied. The fundus of the gallbladder was cannulated with a length of plastic tubing attached to a three-way tap with a syringe and a pressure transducer. At selected widths of 8 mm or less, the cystic duct was secured with a single application of one of the following: (1) a metal clip (Ligacip, Ethicon, Cincinnati, Ohio, USA); (2) a polydioxanone self-locking clip (PDS Absolok; Ethicon); (3) a '0' catgut endoloop (Endoloop; Ethicon); or (4) a '0' polyglactin Roeder knot (Vicryl; Ethicon) tightened with a knot pusher, and at widths of 15 and 20 mm with one of (3) or (4). The duct was then divided either flush or with a 5-mm margin. After immersion in a saline-filled chamber, the gallbladder was inflated with a solution of saline and methylene blue (up to a maximum of 150 mmHg), and the pressure at which any leakage occurred was recorded.

Results

Seventy-two measurements were made on 18 gallbladders (Table 1). With a duct diameter of 8 mm or less, one leak was identified at 110 mmHg; margin size did not affect leakage risk ($n=31$; $P=0.77$, Fisher's exact probability

test), and all four closure methods were of equivalent safety ($n=31$; $\chi^2=2.2$, 3 d.f., $P=0.54$).

The risk of leakage was seen to increase proportionately with increasing duct diameter ($n=72$; χ^2 for trend = 7.7, 1 d.f., $P=0.005$). This was mainly a function of leakage with zero margin ($n=43$; $\chi^2=12.7$, 2 d.f., $P=0.002$); the effect was abolished with a 5-mm margin ($n=29$; $\chi^2=1.7$, 2 d.f., $P=0.43$) and no leak occurred below 100 mmHg under these conditions.

The hydrostatic pressure at which leakage occurred was variable (median 64 (range 20–130) mmHg), but four leaks were found at pressures below 40 mmHg.

Discussion

On a duct of normal calibre, no clip or ligature slipped below a pressure of 110 mmHg, even with flush division. These findings are consistent with the reported physical properties of surgical clips and ligatures^{2–4}.

As expected, the risk of leakage increased in direct relation to duct diameter (Laplace law)⁵. This effect can be abolished if a safety margin of 5 mm is used.

In conclusion, for cystic ducts of 8 mm or less in diameter, a single ligating device with flush division is secure. With a duct diameter greater than 8 mm, a ligature with a 5-mm margin provides safe closure. In either instance, a correctly applied occluding mechanism is unlikely to 'slip off' and failure probably relates to other factors such as diathermy injury.

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Table 1 Duct diameter versus margin and closure type

Duct diameter (mm)	Leak at 150 mmHg	Zero margin		5-mm margin	
		Yes	No	Yes	No
≤ 8	All closures	1	23	0	7
15	Endoloop	0	6	0	7
	Polyglactin knot	3	2	0	4
20	Endoloop	2	3	0	7
	Polyglactin knot	3	0	1	3

Comparison of computed tomography and duplex imaging in assessing aortic morphology following endovascular aneurysm repair

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Background Computed tomography (CT) has been used to assess patients following endovascular aneurysm repair to determine the need for secondary endoluminal or operative procedures. This prospective study compared CT and duplex imaging to evaluate aneurysm morphology following endoluminal aortic grafting.

Methods Twenty patients were evaluated at regular intervals following successful endoluminal aneurysm repair. CT and duplex scanning were compared in their ability to determine aneurysm and aortic diameter, the presence of perigraft extravasation (endoleaks) and technical defects in the endograft.

Results In 20 patients who were assessed 6 months after operation, duplex imaging identified four endoleaks (two early, two late; one proximal, three distal). In three cases, the aneurysm diameter progressively increased after operation. In patients with a thrombosed aneurysm sac, the aneurysm regressed at a median of 0.40 (range 0.13–0.8) cm per year. The CT findings were similar (median regression 0.43 (range 0–1.0) cm per year), although CT was unable to predict the site of the leak as accurately as duplex imaging. CT demonstrated that the diameter of the juxtarenal aorta increased following endografting.

Conclusion Duplex imaging is a less invasive, less costly alternative to CT in the follow-up of patients after endoluminal aortic surgery. Increase in size of the aneurysm sac following endovascular aneurysm repair strongly suggests the presence of an endoleak.

Successful endovascular abdominal aneurysm repair has now been documented by many centres worldwide^{1–4}. It remains unknown whether endovascular repair will abolish the risk of aneurysm rupture, whether current endografts will retain their structural integrity and whether the dilating process will be retarded by successful aneurysm exclusion⁵.

Short-term follow-up of patients who had a technically satisfactory endovascular aneurysm repair revealed a significant incidence of graft-related complications, including structural failure of the endograft⁶, development of leakage between the endograft and the aortic wall (endoleaks)^{7,8} and thrombosis of bifurcated prostheses⁹. The possibility of such complications necessitates the careful surveillance of patients following endoluminal aortic surgery.

Most investigators use computed tomography (CT) to monitor patients following endovascular aortic surgery. CT images both the endograft and the aneurysm sac, and the use of contrast enables the detection of endoleaks^{9–11}. CT is relatively expensive and adds to the cost of endoluminal aneurysm repair. Surveillance may have to continue for several decades, so that the issue of radiation exposure arises.

The aim of this study was to compare duplex imaging and CT in the evaluation of patients following endovascular aneurysm repair.

Patients and methods

Up to December 1996, endovascular aneurysm repair was attempted in 48 patients, with primary success in 43. Twenty of these patients were followed for at least 6 months and formed the group for study. The median age of the patients was 72 (range 68–84) years with a median aneurysm diameter of 5.2 (range 4.8–7.3) cm as measured by CT and 5.0 (4.3–7.0) cm as determined by duplex imaging. Median follow-up was 14 (range 6–31) months. The types of endovascular aneurysm repair included six aortic tube endografts (Endovascular Technologies EGS, Menlo Park, California, USA)^{6,11,12}, three bifurcated systems (Stentor; Mintec, Freeport, Bahamas)¹³ and 11 tapered aortouni-iliac grafts¹⁴.

All patients who had a technically successful endovascular aneurysm repair were entered into a standard prospective surveillance programme at 3, 6, 12, 18 and 24 months following repair. At each visit, patients had a clinical examination followed by CT and duplex imaging. Diagnostic imaging was performed by investigators (G.F. and T.H.) who were blinded of the result from the other imaging technique and previous scans. Details were recorded as to the presence or absence of flow within the aneurysm sac (endoleak), the maximum diameter of the aneurysm sac in any orientation and any technical defects in the endoprosthesis. The juxtarenal diameter was quantified on the CT scans alone.

Duplex imaging was performed with the patient supine using a 3.5-MHz curved linear array transducer, HDI Ultramark 9 (ATL, Letchworth, UK). Colour Doppler ultrasonography was utilized to image flow within the graft, and any flow disturbance was noted. Endoleaks were specifically sought with the colour Doppler set to detect low flow.

CT was done using a Siemens HiQ scanner (Munich, Germany). An initial tomogram determined the cranial extent of the proximal metallic stent. Some 30 s following the intravenous injection of contrast, serial 10-mm slices were performed from the renal arteries to the level of the femoral head. The endograft was imaged to determine the presence of thrombus within the

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graft lumen. Endoleaks were defined by the presence of contrast within the aneurysm sac, and an attempt was made to determine the site of any leak.

Results

Detection of endoleaks

Dynamic CT demonstrated four cases of perigraft contrast extravasation (Fig. 1). Two of the endoleaks were present on the immediate postoperative scan; the other two developed 6 months later. One leak was at the proximal stented anastomosis and the remaining three involved the distal part of the aneurysm sac, although the specific site could not be demonstrated.

Similarly, duplex imaging demonstrated the presence of flow within the aneurysm sac at the site of the leak in the same four patients at identical times (Fig. 2). Duplex imaging was, however, able to localize the specific site of the distal leak in all cases. One patient with a straight endograft had a leak originating from the distal aortic stent, whereas two with aortouni-iliac grafts had a retrograde jet of blood leaking from a common iliac artery which had been ligated or embolized during endovascular repair. All three patients with distal

endoleaks had secondary procedures. The aortic tube graft was revised to a conventional aneurysm repair, whereas the two leaks from common iliac arteries were successfully treated by endoluminal coil embolization. The patient with a proximal leak was deemed unfit for surgical revision and continues in the surveillance programme.

Aneurysm diameter

The change in aneurysm diameter following endovascular repair was analysed separately in patients with and without evidence of perigraft flow within the aneurysm sac. Of the four patients with a proven endoleak, three had an increase in aneurysm diameter on both CT and duplex imaging (Fig. 3). The patient with no increase in aneurysm diameter had an endoleak detected at 6 months following a normal 3-month scan. The endoleak was

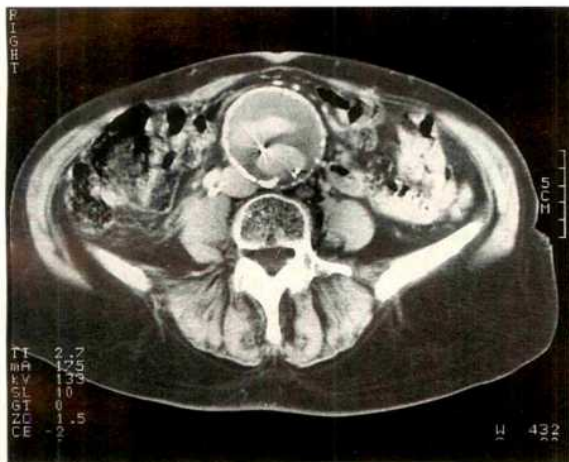


Fig. 1 Computed tomogram demonstrating perigraft extravasation of contrast into aneurysm sac



Fig. 2 Colour duplex scan demonstrating flow within the aneurysm sac

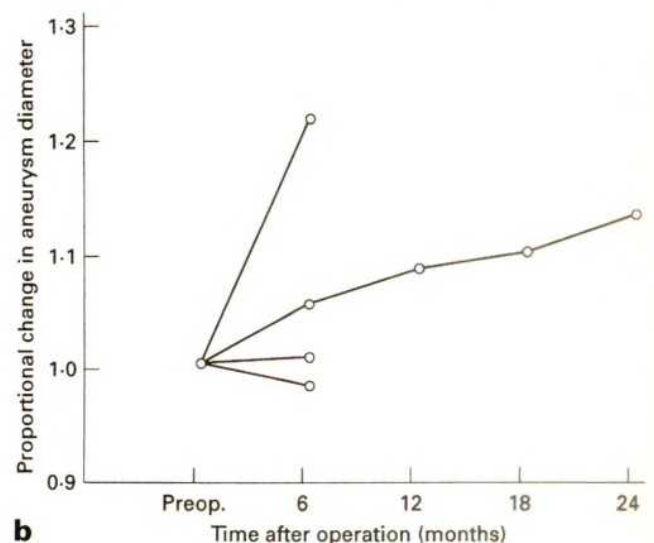
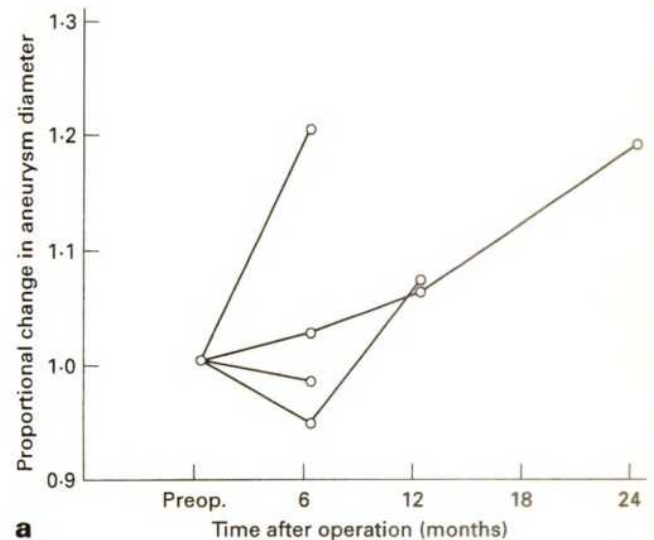


Fig. 3 Proportional change in aneurysm diameter in four patients with a proven endoleak as determined by a computed tomography and b duplex imaging

embolized immediately and it remains unknown whether this aneurysm would have expanded if untreated.

Patients with a technically satisfactory endovascular aneurysm repair had thrombosis and regression of the aneurysm sac. Measurements obtained from CT revealed aneurysm regression in 15 of 16 patients, whereas aneurysm diameter quantified by duplex scanning diminished in all 16 patients with no evidence of endoleak (Fig. 4). Median (range) aneurysm regression was 0.43 (0–1.0) and 0.40 (0.13–0.8) cm per year by CT and duplex imaging respectively.

The 95 per cent level of agreement between CT and duplex imaging was calculated¹⁵ to be between –0.73 and 1.25 cm. The 95 per cent confidence interval for the difference between the two imaging techniques was –0.11–0.41. As zero lies between this confidence interval, it may be assumed that there was a constant bias between the two techniques, with CT giving consistently larger diameters than duplex imaging.

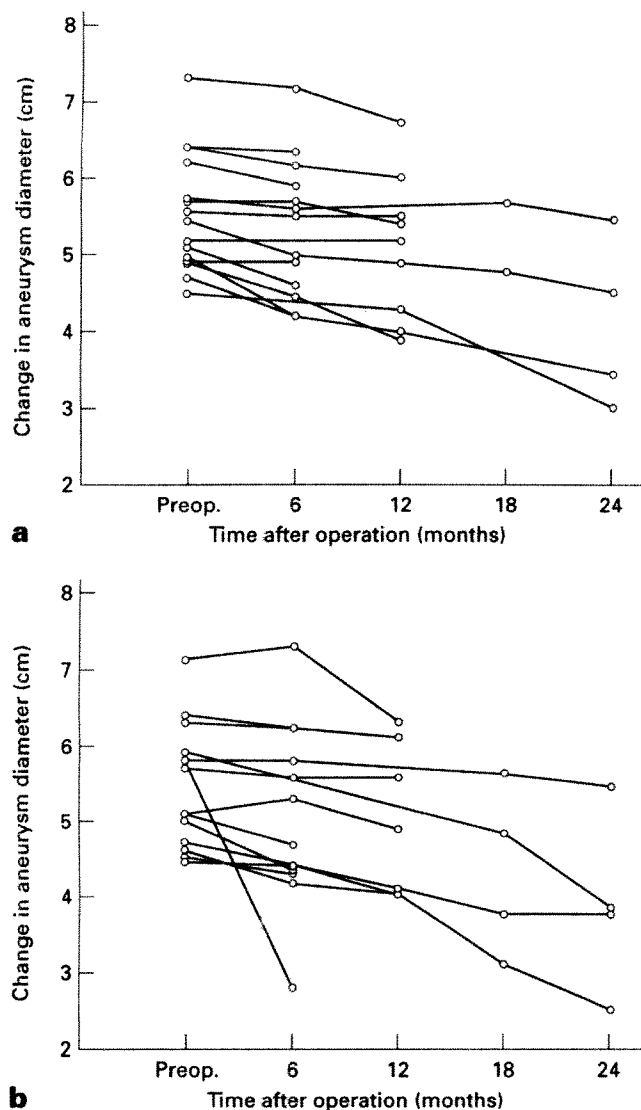


Fig. 4 Change in aneurysm diameter in patients with technically satisfactory endovascular aneurysm repair as determined by a computed tomography and b duplex imaging

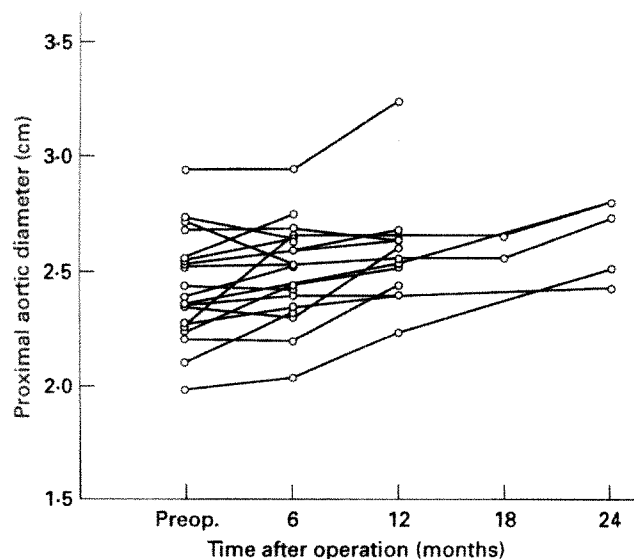


Fig. 5 Change in proximal aortic diameter following endovascular aneurysm repair

Technical defects

Abnormal flow patterns were found within the endograft on duplex imaging in one aortouni-iliac reconstruction. CT suggested the presence of thrombus within the tapered portion of the graft, and a subsequent arteriogram confirmed a twist within the graft which was treated by placement of an endoluminal stent.

Diameter of the juxtarenal aorta following endovascular aneurysm repair

The diameter of the juxtarenal aorta following endovascular aneurysm repair expanded gradually during follow-up (Fig. 5), with a median increase of 0.16 (range 0.04–0.3) cm per year. The increase in aortic diameter did not appear to be confined to the immediate perioperative period, but was progressive and still evident 24 months after surgery.

Discussion

The relatively high incidence of complications following endovascular aneurysm surgery mandates a rigorous postoperative surveillance programme. Endoleaks have been described in all initial series of endovascular aneurysm repairs^{2–4,11,16,19}, with an incidence ranging from 10 to 43 per cent. Endoleaks may be early or late, and may arise from the proximal anastomosis, the distal anastomosis, or as a result of retrograde filling from the lumbar, inferior mesenteric or common iliac vessels. Irrespective of the origin of the leak, the consequences are potentially serious. Establishment of flow within the aneurysm sac may facilitate continued aneurysm expansion and eventual rupture^{4,17}. It is essential that endoleaks are detected by a postoperative surveillance programme to allow early correction.

Conventionally, CT has been used to follow patients after endovascular aneurysm repair. Recent studies have suggested that duplex imaging may be useful in this setting^{2,11}. The present prospective study compared CT and duplex imaging in the evaluation of patients following

endovascular aneurysm surgery. There was no difference in the ability of the two imaging methods to demonstrate flow within the aneurysm sac, although duplex imaging was superior in demonstrating the site of the endoleak. The 95 per cent limits of agreement between CT and duplex imaging were similar to those reported by Lederle *et al.*¹⁸, who also reported that CT gives a larger estimate of aneurysm diameter than ultrasound-based methods.

Data from the present study revealed that the majority of patients with a proven endoleak had continued expansion of the aneurysm sac. This has been observed in other studies. May *et al.*¹⁶ reported five patients with perigraft extravasation; all had increasing aortic diameter. However, contrary to these findings, Moore and Rutherford¹¹ reported six patients with chronic endoleaks with no evidence of aneurysm enlargement. Further follow-up is required to document the natural history of endoleaks following endovascular aneurysm repair.

Results from this study and that of May *et al.*¹⁶ suggest that successful exclusion of the aneurysm sac results in a reduction of aneurysm size. It would be anticipated that the reduction in aneurysm size associated with successful endovascular aneurysm repair would be translated into a reduction in the risk of aneurysm rupture. Support for this concept comes from Resnikoff *et al.*²⁰, who described the fate of 831 patients following operative exclusion of the aneurysm sac. From this cohort of patients only 17 aneurysms (2 per cent) remained patent, and of these only two developed sac rupture.

One theoretical problem associated with endovascular aneurysm repair concerns the fate of the proximal aortic neck^{5,21}. Aneurysmal disease is a general dilating process in which all the arteries in the body are enlarged^{22,23}. The proximal aortic neck may continue to dilate, which could cause migration and displacement of the proximal aortic stent. The present study demonstrated that the aorta at the level of the renal arteries does continue to dilate progressively, at least for up to 2 years after surgery. Similarly, May *et al.*¹⁶ demonstrated initial expansion of the supraceliac aorta following endovascular aneurysm repair but suggested that the process was not progressive. The occurrence of aneurysms above existing aortic grafts²⁴ suggests that aortic dilatation is not retarded by conventional aneurysm repair. Baker *et al.*²⁵ have quantified dilatation of the proximal aortic neck after conventional surgery. If the aortic expansion is progressive, stent design will need to allow for this²⁶.

The present study has demonstrated that duplex imaging may be used as the first-line investigation to monitor patients following endovascular aneurysm repair. Cross-sectional imaging may then be reserved for patients with a demonstrable endoleak or increase in aneurysm diameter. The reduction in aortic diameter that accompanies successful endoluminal repair suggests that this technique may be effective in preventing aneurysm rupture. The progressive enlargement of the proximal aorta has serious implications for the long-term durability of aortic endografts.

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Influence of graft material on blood rheology and plasma biochemistry following insertion of an infrainguinal bypass graft

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Background Occlusive arterial disease causes alterations in blood rheology and levels of potential thrombotic and fibrinolytic mediators. The aim of this study was to investigate the effect of graft materials on these parameters in patients undergoing successful infrainguinal revascularization

Methods Some 186 consecutive infrainguinal grafts were observed for 12 months. Venous blood was sampled before operation and at 3, 6, and 12 months after surgery. Samples were assayed for thrombotic and rheological parameters. An area under the curve analysis was used to compare the effects of vein and synthetic grafting on these parameters in 99 patients whose grafts remained patent and free from stenosis.

Results Plasma levels of fibrin degradation products were significantly higher in patients with synthetic grafts ($n = 46$) than in those with autogenous vein grafts ($n = 53$) (median 274 versus 150 ng/ml; $P < 0.001$). There were no significant differences in plasma fibrinogen or any other parameters between the two groups.

Conclusion Patients with a synthetic infrainguinal graft have a higher fibrin turnover than those with a vein graft. Further studies are required to determine whether this increase in fibrin turnover is an essential requirement to maintain patency of a synthetic infrainguinal graft.

A number of studies have shown an association between altered levels of fibrinogen and the outcome of infrainguinal bypass grafting^{1–3}. The authors⁴ have reported previously that levels of rheological variables and thrombotic mediators predict the outcome following infrainguinal revascularization, and that plasma fibrinogen levels fall following resolution of critical limb ischaemia⁵. There is also evidence that levels of plasma fibrinogen and other potential thrombotic mediators are raised in patients whose grafts develop postoperative stenosis or occlusion^{6,7}. This study was undertaken to investigate the effects of graft material on blood rheology, plasma fibrinogen and fibrin turnover, and a number of thrombotic and fibrinolytic parameters in patients undergoing successful infrainguinal revascularization.

Patients and methods

Venous blood was sampled without stasis in a consecutive series of 186 patients who had an infrainguinal bypass graft inserted during 18 months in two vascular surgical units. Samples were assayed for plasma and whole blood viscosity, red cell aggregation, white blood cell and platelet counts, plasma fibrinogen, fibrin degradation products (FDP d-dimer), von Willebrand factor (vWf), plasminogen activator inhibitor, tissue plasminogen activator and factor VII as described previously^{8,9}.

All patients had venous sampling before surgery as part of another study⁴, and in addition at 3, 6 and 12 months after operation. Colour duplex imaging was also performed at these time points to detect graft stenosis or occlusion. Any new thrombotic events (myocardial infarction, development of atrial fibrillation, stroke or transient ischaemic attack, development of critical limb ischaemia) or changes in medication since last attendance were recorded. Some grafts underwent impedance analysis and direct insonation as part of a postoperative surveillance programme¹⁰. Arteriography was performed for any

graft in which the results of surveillance investigations were abnormal. The graft material employed for revascularization was chosen at the discretion of the operating surgeon although it was standard practice during the study to use suitable ipsilateral leg vein where available, in preference to synthetic material.

Statistical analysis

The serial rheology and plasma biochemistry results were plotted for individual patients, and areas under the curve calculated for each patient based on linear interpolation between time points. The area was scaled in each case depending on the duration of data available. This led, for each patient, to a single weighted average of their available data. Only patients with a baseline measurement and at least two postoperative measurements were analysed. The term 'area' therefore refers to the area scaled according to the duration of available data, and is expressed in terms of the original units of measurement for each variable studied¹¹.

Patients who died during the 12-month follow-up, who developed new potentially thrombotic events, or who began anticoagulant therapy following surgery were excluded from the analysis, as were data from any patient whose graft occluded or developed an angiographically proven stenosis. The Mann–Whitney *U* test was used to compare the adjusted areas under the curve for patients whose grafts remained patent for 1 year.

Results

Ninety-nine infrainguinal grafts in 99 patients (70 men and 29 women) were available for analysis, 53 vein and 46 synthetic grafts. All the synthetic grafts were 6-mm diameter polytetrafluoroethylene (PTFE; GORE-TEX, W. L. Gore, Woking, UK; Impira-flex, Impira, Droitwich, UK). Details of the 87 grafts excluded from the analysis are given in Table 1; the 1-year outcome for the entire series of 186 grafts has been reported in detail elsewhere⁴.

The median age of patients in this study was 65 (interquartile range (i.q.r.) 59–70) years. There were no

significant differences in age ($P=0.15$, Mann-Whitney U test), sex ($P=0.26$, 1 d.f., χ^2 test) or smoking habit ($P=0.37$, 1 d.f., χ^2 test) between patients who had vein or synthetic grafts (Table 2).

Table 1 Details of the 87 grafts excluded from the analysis

Reason for exclusion	No. of grafts excluded
Graft occlusion during study interval	50
Death during study	17
Dacron graft [†]	7
Vein graft stenosis	6
Prosthetic graft infection	2
Patient lost to follow-up (graft patent) [†]	2
Commenced anticoagulation	2
New thrombotic event during study	1
Total	87

*Excluded to provide homogeneous group of polytetrafluoroethylene synthetic grafts for comparison with vein. [†]Confirmed by general practitioner

Table 2 Clinical details

	Vein grafts ($n=53$)	Synthetic grafts ($n=46$)
Median age (years)*	64 (56–69)	68 (61–71)
Men	40 (75)	30 (65)
Women	13 (25)	16 (35)
Non-smoker [†]	13 (25)	15 (33)
Current/ex-smoker	40 (75)	31 (67)

Values in parentheses are percentages or *interquartile ranges. [†]Not smoked for at least 5 years; normal carboxyhaemoglobin level throughout the study

Analysis of the adjusted areas under the curve for the rheological and biochemical variables showed no significant differences between patients with vein or synthetic grafts (Table 3), with the exception of cross-linked FDP. Levels of these were significantly higher in patients with a patent synthetic graft than in those with a vein graft ($P=0.0004$) (Fig. 1). There was no significant difference in preoperative levels of FDP between patients who had vein (median 137 (i.q.r. 102–270) ng/ml) or synthetic (180 (110–280) ng/ml) grafts.

Discussion

Recent studies have suggested that raised levels of plasma fibrinogen and vWf adversely affect revascularization surgery with both vein and synthetic grafts^{1–4}. Most graft surveillance programmes rely on the fact that stenoses can often be identified in vein grafts before occlusion, offering the potential for preventative treatment to maintain patency^{12,13}. However, synthetic graft occlusion is probably thrombotic in origin and few surveillance programmes have been able to identify the failing synthetic graft before occlusion¹⁰.

This study documents the effects of graft material on thrombotic and fibrinolytic parameters. Analysis was restricted to patients with patent grafts that were free from stenoses, and who did not suffer any new (potentially thrombotic) cardiovascular or cerebrovascular events during follow-up. It is likely that any differences in potential thrombotic mediators are the result of the graft material employed.

Comparison of the adjusted areas under the curve for the rheological and thrombotic parameters studied indicated that the use of a synthetic graft did not result in a more 'thrombogenic environment' than the use of autogenous vein. Although the synthetic grafts came from two different manufacturers they were all made from expanded PTFE. The observations made in this study reflect the effects of this particular graft material.

Table 3 Adjusted areas under the curve for haematological, rheological and biochemical parameters in patients with vein and synthetic grafts

Variable	Vein grafts		Synthetic grafts		P^*	95% Confidence interval for difference in median areas (vein – synthetic)
	n	Area	n	Area		
Platelet count ($\times 10^9/l$)	51	245 (215–284)	43	233 (217–255)	0.22	(–7.9 to 31.6)
White cell count ($\times 10^9/l$)	51	7.7 (6.5–8.9)	43	7.4 (6.6–9.0)	0.98	(–0.65 to 0.71)
Plasma viscosity (mPa s)	43	1.33 (1.29–1.37)	41	1.34 (1.27–1.40)	0.27	(–0.046 to 0.016)
Whole blood viscosity (mPa s)	44	3.24 (2.97–3.54)	37	3.16 (2.98–3.59)	0.63	(–0.245 to 0.144)
Red cell aggregation (units)	43	4.1 (3.3–4.9)	39	4.2 (3.8–5.1)	0.34	(–0.69 to 0.21)
Corrected blood viscosity (mPa s)	39	3.28 (3.05–3.44)	34	3.41 (3.11–3.50)	0.30	(–0.178 to 0.055)
Relative blood viscosity	39	2.45 (2.32–2.57)	34	2.45 (2.37–2.54)	0.90	(–0.088 to 0.070)
Haematocrit (%)	45	44 (42–47)	39	44 (41–46)	0.66	(–1.5 to 2.1)
Plasma fibrinogen (g/l)	50	3.4 (3.0–3.9)	43	3.2 (2.9–3.8)	0.30	(–0.149 to 0.452)
FDP (ng/ml)	51	150 (92–238)	43	274 (204–371)	0.0004	(–158.0 to –49.3)
von Willebrand factor (iu/dl)	51	122 (87–146)	43	130 (84–174)	0.89	(–22.1 to 16.4)
Tissue plasminogen activator (ng/ml)	45	8.9 (7.2–10.7)	39	9.9 (7.4–11.8)	0.19	(–2.14 to 0.42)
Factor VII (% pool)	48	107 (88–115)	42	107 (97–121)	0.38	(–12.8 to 4.1)
PAI (% pool)	42	110 (91–134)	40	123 (97–147)	0.27	(–24.0 to 6.6)

Values are median (interquartile range). Analysis of individual variables was performed using only patients who had a baseline level and at least two follow-up measurements recorded for that variable, this accounts for the differences in number of patients analysed for each variable. FDP, fibrinogen degradation products; PAI, plasminogen activator inhibitor; iu, international units. *Mann-Whitney U test

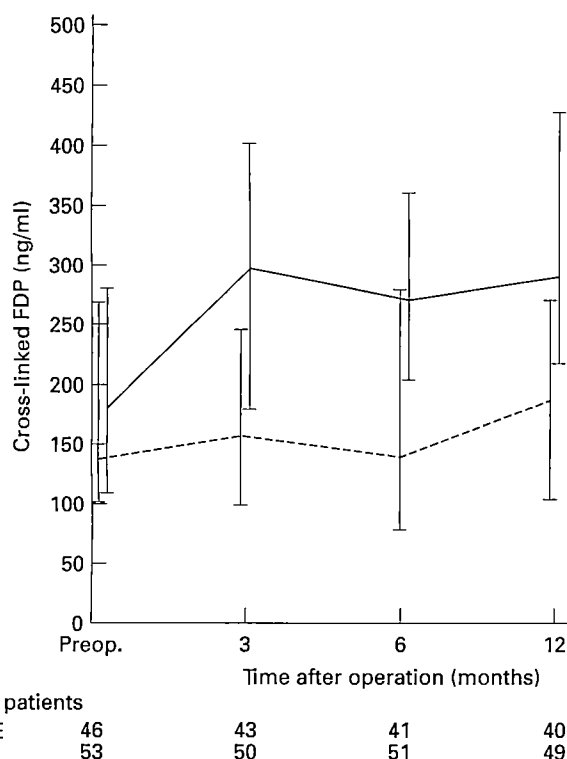


Fig. 1 Change in levels of fibrin degradation products (FDP) in 53 vein (----) and 46 polytetrafluoroethylene (PTFE) (—) infrainguinal grafts. Values are median (interquartile range)

The only apparent difference in patients with a synthetic graft was that levels of FDP were greater in the 12 months following insertion than in patients with vein grafts. This indicates that fibrin turnover was significantly greater in patients with synthetic grafts. Synthetic grafts are known to be covered in a layer of fibrin often referred to as a pseudointima¹⁴; complete endothelialization of the graft surface does not occur¹⁵. It can be assumed that there is a continuous dynamic turnover of this fibrinous pseudointima. An increase in formation and lysis of cross-linked fibrin within a synthetic graft lumen may be required to prevent thrombotic occlusion due to an accumulation of this fibrinous pseudointima. This would lead to an increase in levels of FDP in patients with a synthetic graft that would not be observed in patients with an endothelialized vein graft. Increased plasma fibrinolysis may not be confined to synthetic infrainguinal grafts as levels of FDP are also increased immediately following aortic grafting with synthetic material¹⁶.

While differing degrees of surgical trauma might produce different levels of FDP after operation, it is unlikely that surgical trauma would produce a consistent increase in levels beyond the first few postoperative months. There is unlikely to be significant difference in the degree of surgical trauma between the two groups studied, as a tunneller was passed through the thigh to position both vein and PTFE grafts. The limited exposure required for PTFE grafting, however, may result in less tissue trauma than vein harvesting.

Increased fibrin turnover may be an essential requirement to maintain patency of a synthetic graft. Synthetic graft occlusion may occur when it is no longer possible to maintain this increased fibrinolysis. If this is

the case, a fall in levels of FDP after operation may identify patients whose synthetic grafts are at risk of occluding and who might benefit from anticoagulation. Prospective studies are required to investigate this issue.

Raised levels of FDP are associated with an increased risk of coronary heart disease¹⁷ and are independently related to the severity of arterial disease⁹. Although these observations may reflect thrombus formation during the progression of arterial disease rather than a causal relationship, there is some evidence that FDPs have mitogenic activity within atherosclerotic plaques¹⁸, can stimulate hepatic fibrinogen synthesis¹⁹, and can also stimulate the release of endothelial cell-derived growth factors²⁰. Anything which increases levels of FDP might lead to accelerated atherosclerosis in both peripheral and coronary arteries by creating a more atherogenic environment. Follow-up studies are therefore required to determine whether the increased levels of FDP associated with synthetic grafts result in accelerated progression of atherosclerosis.

The use of a synthetic PTFE infrainguinal graft is associated with an increase in levels of FDP that is not seen following use of autogenous vein. This increase in fibrin turnover may be related to an obligatory lysis of fibrin deposited within the lumen of synthetic grafts. Further studies are required to determine whether this is an essential requirement to maintain patency of PTFE grafts.

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Risk factors for anastomotic leakage after resection of rectal cancer

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Background The most important surgical complication following rectal resection with anastomosis is symptomatic anastomotic leakage, which is associated with a 6–22 per cent mortality rate. The aim of this retrospective study was to evaluate the risk factors for clinical anastomotic leakage after anterior resection for cancer of the rectum.

Methods From 1980 to 1995, 272 consecutive anterior resections for rectal cancer were performed by the same surgical team; 131 anastomoses were situated 5 cm or less from the anal verge. The associations between clinical anastomotic leakage and 19 patient-, tumour-, surgical- and treatment-related variables were studied by univariate and multivariate analysis.

Results The rate of clinical anastomotic leakage was 12 per cent (32 of 272). Multivariate analysis of the overall population showed that only male sex and level of anastomosis were independent factors for development of anastomotic leakage. The risk of leakage was 6.5 times higher for anastomoses situated less than 5 cm from the anal verge than for those situated above 5 cm; it was 2.7 times higher for men than for women. In a second analysis of low anastomoses (5 cm or less from the anal verge; $n = 131$), obesity was statistically associated with leakage.

Conclusion A protective stoma is suitable after sphincter-saving resection for rectal cancer for anastomoses situated at or less than 5 cm from the anal verge, particularly for men and obese patients.

The most important surgical complication following rectal resection with intestinal anastomosis is symptomatic anastomotic leakage. The clinical leakage rate after anterior resection varies from 3 to 19 per cent^{1–15}, and the mortality rate and risk of permanent stoma after clinical leakage are 6–22 per cent^{1,4,7,8,10,12–14,16} and 10–100 per cent^{7,8,10,12,13} respectively.

The aim of this retrospective study was to evaluate the risk factors for clinical anastomotic leakage in patients who had rectal resection for cancer.

Patients and methods

Patients

Consecutive patients who underwent rectal resection for cancer with a colorectal or coloanal anastomosis between 1 January 1980 and 31 December 1995 were included in the study. Patients having repeated resection for local recurrence of rectal cancer and colorectal anastomosis after Hartmann's procedure were excluded.

Surgical procedure

All patients were operated on by the same surgical team, more than half (56 per cent) by the senior author (M.P.). The day before operation, bowel lavage with 3 litres of polyethylene glycol was carried out, and all patients received antibiotic prophylaxis for a minimum of 2 days. A midline abdominal incision was performed. The inferior mesenteric artery was ligated at its origin flush with the aorta or just below the ascending left colic artery. The left colon and splenic flexure were mobilized in the majority of low anterior resections to achieve anastomosis without tension. The sigmoid or descending colon was transected. Rectal dissection was carried out 5 cm below the lower edge of tumours in the upper third of the rectum, and to the pelvic floor for mid and low rectal tumours¹⁷. Rectal irrigation was performed during operation, before

transection of the rectum, using povidone–iodine solution for most patients. When the tumour was very low, partial resection of the anal canal was performed by the abdominal approach, or by the perineal approach after everting the anal canal. Minimal distal clearance of the tumour on the fresh specimen was 2 cm.

Anastomoses were hand-sewn or stapled (EEA; CEEA; US Surgical, Norwalk, Connecticut, USA). The doughnuts were always inspected for completeness. Anastomotic integrity was tested during operation by transanal instillation of fluid only for low anastomoses, particularly if there were difficulties in performing the anastomosis or if the doughnuts were incomplete. A colonic J pouch was sometimes used. A protective colostomy or ileostomy was used if there was anastomotic tension, poor bowel preparation, incomplete doughnuts or leakage on testing, or technical difficulties in performing low rectal anastomosis because of the anatomy of the patient, and for all coloanal anastomoses. Pelvic drains, placed behind the anastomosis in the presacral space, were always used.

Some patients who had a tumour with a high risk of local recurrence received preoperative and sometimes intraoperative radiotherapy.

Definition of anastomotic leakage

The definition of anastomotic leakage in the present study was clinical: gas, pus or faecal discharge from the drain, pelvic abscess, peritonitis, discharge of pus per rectum or rectovaginal fistula. All anastomotic leakages were confirmed by water-soluble contrast enema, performed by the surgeon. Extra-anastomotic complications (leak at the apex of the efferent limb of the J pouch, two cases; pelvic abscess without leakage, one case) were not considered as clinical anastomotic leakage. Asymptomatic radiological anastomotic leakages were not considered because routine contrast enema was not performed after operation. Patients who died from general postoperative complications ($n = 5$) before the mean date of clinical anastomotic leakage were considered as unevaluable, and were excluded from the study.

Statistical analysis

A first analysis was carried out on the overall population of patients who had colorectal or coloanal anastomoses. A second

analysis was performed only on patients with anastomoses 5 cm or less from the anal verge.

Sixteen independent variables were analysed: age, sex, obesity (20 per cent heavier than ideal body-weight), tumour height

(distance between tumour caudal edge and the anal verge), tumour stage (tumour node metastasis (TNM) classification¹⁶), level of ligation of the inferior mesenteric artery, type of colon used for anastomosis, level of anastomosis from the anal verge,

Table 1 Anastomotic leakage after resection of rectal cancer – univariate analysis

	Overall population (<i>n</i> = 272)		Low anastomoses (<i>n</i> = 131)	
	No. of patients	<i>P</i>	No. of patients	<i>P</i>
Sex				
M	25 of 165 (15)	0.03	18 of 75 (24)	0.09
F	7 of 107 (7)		7 of 56 (12)	
Obesity*				
Yes	9 of 54 (17)	0.16	9 of 27 (33)	0.03
No	20 of 204 (10)		15 of 99 (15)	
Tumour height (cm)				
12.5–18	2 of 54 (4)	0.11	—	0.43
6.5–12	22 of 166 (13)		17 of 80 (21)	
3–6	8 of 52 (15)		8 of 51 (16)	
Tumour stage				
T ₁₋₂	8 of 80 (10)	0.56	6 of 43 (14)	0.30
T ₃₋₄	24 of 192 (12)		19 of 88 (22)	
Inferior mesenteric artery				
High ligation	8 of 66 (12)	0.92	6 of 38 (16)	0.54
Low ligation	24 of 206 (12)		19 of 93 (20)	
Colonic section level*				
Sigmoid	21 of 163 (13)	0.37	16 of 82 (20)	0.69
Descending	10 of 107 (9)		8 of 48 (17)	
Level of anastomosis (cm)				
8.5–15	0 of 44 (0)	0.002	—	0.99
5.5–8	7 of 97 (7)		—	
3.5–5	16 of 84 (19)		16 of 84 (19)	
1.0–3	9 of 47 (19)		9 of 47 (19)	
Type of anastomosis				
Hand-sewn	10 of 121 (8)	0.11	6 of 44 (14)	0.26
Stapled	22 of 151 (15)		19 of 87 (22)	
Configuration of anastomosis				
End to end	23 of 152 (15)	0.08	18 of 86 (21)	0.42
Side to end	8 of 110 (7)		6 of 41 (15)	
End to side	0 of 10 (0)		0 of 4 (0)	
Protective stoma				
Yes	20 of 114 (18)	0.01	16 of 86 (19)	0.85
No	12 of 158 (8)		9 of 45 (20)	
Preoperative radiotherapy				
Yes	4 of 28 (14)	0.66	4 of 25 (16)	0.66
No	28 of 244 (11)		21 of 106 (20)	
Intraoperative radiotherapy				
Yes	4 of 19 (21)	0.19	4 of 17 (24)	0.62
No	28 of 253 (11)		21 of 114 (18)	
Quality of resection				
Curative	29 of 239 (12)	0.61	23 of 121 (19)	0.94
Palliative	3 of 33 (9)		2 of 10 (20)	
Length of intervention (h)				
≤ 4	11 of 148 (7)	0.01	8 of 46 (17)	0.72
> 4	21 of 124 (17)		17 of 85 (20)	
Operator				
Colorectal surgeon	29 of 204 (14)	0.03	24 of 113 (21)	0.12
Digestive surgeon	3 of 68 (4)		1 of 18 (6)	
Colonic pouch				
Yes	—		3 of 19 (16)	0.77
No	—		22 of 112 (20)	
Anal canal resection				
Yes	—		4 of 22 (18)	0.90
No	—		21 of 109 (19)	
Anal canal eversion				
Yes	—		2 of 10 (20)	0.95
No	—		23 of 121 (19)	

Values in parentheses are percentages. *Clinical data not complete for all patients. Age was not associated with leakage for the overall population (*P* = 0.95) or for those with low anastomoses (*P* = 0.60)

Table 2 Features of clinical anastomotic leakage after resection of rectal cancer

	No. of patients
Gas, pus or faecal discharge from drain	21
Pelvic abscess	3
Peritonitis	2
Discharge of pus per rectum	2
Rectovaginal fistula	4
Total	32

type of anastomosis (stapled or sutured), configuration of anastomosis (end to end, end to side or side to end), protective stoma, preoperative radiotherapy, intraoperative radiotherapy, quality of resection (curative *versus* palliative), length of intervention, and operator (colorectal *versus* digestive surgeons). For the second analysis, three other variables were included colonic pouch, anal canal resection and anal canal eversion.

The association of leakage and independent variables was studied by univariate analysis (χ^2 test, Student's *t* test and Fisher's exact test for small groups). All variables associated with leakage with $P \leq 0.2$ were considered for multivariate analysis. Multiple logistic regression was first done on this full model. Variables were eliminated one at a time, beginning with the variable having the highest *P* value. $P \leq 0.05$ was considered significant.

Results

Patients

The first analysis included 272 patients with rectal resection. There were 165 men and 107 women (sex ratio 1.5) with a mean (s.d.) age of 64 (12) (range 25–91) years. Some 239 procedures (88 per cent) were curative and 33 (12 per cent) were palliative.

The second analysis concerned 131 patients with low anastomoses: 75 men and 56 women (sex ratio 1.3) of mean (s.d.) age 63 (11) (range 25–83) years. Details of the clinical characteristics of the two groups are shown in Table 1.

Anastomotic leakage

The rate of clinical anastomotic leakage was 12 per cent (32 of 272) in the overall population of patients having rectal resection, and 19 per cent (25 of 131) in the group with low anastomoses. No patient with anastomosis more than 8 cm from the anal verge had leakage. The mean postoperative period of diagnosis for clinical leakage was 11 (range 2–41) days. The different types of clinical anastomotic leakage are presented in Table 2; the majority were minor leakages.

In the first study (all anastomoses; $n = 272$), univariate analysis showed five variables to be associated with the risk of anastomotic leakage: sex ($P = 0.03$), level of anastomosis ($P = 0.002$), stoma ($P = 0.01$), length of intervention ($P = 0.01$) and operator ($P = 0.03$) (Table 1). Multivariate analysis showed that only sex and level of anastomosis were independent associated factors for the development of anastomotic leakage. The risk of leakage was 2.7 times higher for men than for women ($P = 0.03$; 95 per cent confidence interval (c.i.) 1.07–6.76). It was 6.5 times higher for anastomoses situated at or below 5 cm from the anal verge than for those higher than 5 cm ($P < 0.001$; 95 per cent c.i. 2.37–17.87).

In the second analysis (low anastomoses, $n = 131$), obesity was significantly associated with leakage

($P = 0.03$), and sex was not far from the level of significance ($P = 0.09$) (Table 1). The anastomotic leakage rate after low colorectal and coloanal anastomoses was 33 per cent (nine of 27) for obese patients and 15 per cent (15 of 99) for non-obese patients. It was 24 per cent (18 of 75) for men and 12 per cent (seven of 56) for women.

Leakage and reoperation

Of the 32 patients with clinical anastomotic leakage, 13 had a second surgical intervention. The risk of reoperation was two times greater for patients without a stoma than for those with a stoma (seven of 12 *versus* six of 20, $P = 0.31$). One patient died after leakage. A 66-year-old man had a coloanal anastomosis for a low Dukes C2 rectal cancer. A protective, but unfortunately not defunctioning, stoma was performed with transverse colon. Peritonitis appeared on day 6 after operation. The anastomosis was removed, and excision of the anal canal and a definitive stoma were carried out. The patient died 23 days after reoperation from myocardial infarction.

Discussion

The relatively high rate of clinical anastomotic leaks of 12 per cent in this series, compared with 3–19 per cent reported in recent studies^{1–15}, is due to the fact that about half (48 per cent; 131 of 272) of the anastomoses in the present series were very low, situated 5 cm or less from the anal verge, and because sphincter-saving resection for narrow pelvis, obese patients or very low tumours was rarely avoided¹⁹. However, the postoperative mortality rate after clinical anastomotic leakage was low (one patient), the majority of leakages were minor, and no patient had leakage from an anastomosis situated more than 8 cm from the anal verge.

Colorectal surgeons (M.P. and E.R.) had a higher rate of leakage than other surgeons (J.S. and junior digestive surgeons) because they performed the majority of low colorectal anastomoses and all coloanal anastomoses. Stoma formation and operating time were associated with increased risk of leakage in univariate analysis but were not found to be independent factors of leakage in multivariate analysis, because protective stoma and long operations were often associated with low anastomosis, which was the most important predictive factor for leakage. In the second analysis, performed only with low anastomoses, the leakage rate was the same with or without a stoma (19 *versus* 20 per cent, $P = 0.85$) and after a short or a long operation (17 *versus* 20 per cent, $P = 0.72$).

Level of anastomosis, male sex and obesity were significantly associated with anastomotic leakage. These results suggest that these patient-related variables are more important than surgeon-related variables for risk of clinical leakage after sphincter-saving resection for rectal cancer.

Most studies that have compared high and low anterior resection have shown that, apart from emergency presentation (obstruction, perforation), the level of anastomosis is the most important predictive factor for leakage^{1,2,4,6,10,12–15}. The high-risk level for anastomotic leakage was less than 7 cm from the anal verge for Pakkastie *et al.*¹³, less than 6 cm for Karanjia *et al.*¹² and below 5 cm for Heald and Leicester².

Analysis of the literature shows that it is difficult to associate some variables with the risk of leakage, because

studies rarely report the results of multivariate analysis. Thus, the contribution of the level of anastomosis, which may confound any other relationship, could not be studied. Moreover, most series reporting an analysis of factors associated with leakage include colonic with rectal resections^{1, 2, 6, 8, 13, 15, 16, 20}. On the other hand, some multi-centre studies have shown that the surgeon could be a risk factor for leakage^{1, 21}. This is due to specific technical factors that make anastomosis safe: bowel preparation, pelvic haemostasis, colonic blood supply, anastomotic tension, complete doughnuts and intraoperative testing of the anastomosis^{22–27}. The present authors therefore believe that the level of anastomosis, the type of patient (sex and obesity) and specific technical difficulties are the major risk factors for anastomotic leakage after rectal resection.

Use of a protective stoma in colorectal anastomoses seems not to decrease the leakage rate^{4, 5, 7, 12, 13, 23}, but it does reduce the risk of reoperation and postoperative death if leakage is present^{21, 23, 28}. For this reason, the majority of authors^{5, 7, 12, 14, 20, 21, 26, 28} recommend creating a protective stoma after anterior resection for patients with a high risk of anastomotic leakage. High anterior resections (anastomosis greater than 8 cm from the anal verge) are considered as colonic resections^{1, 21}; the leakage rate is low (zero in the present study) and a stoma is not useful. The high-risk population is limited to those undergoing low anterior resection.

Based on this experience, the authors recommend creating a protective stoma after sphincter-saving resection for rectal cancer for all anastomoses situated 5 cm or less from the anal verge, in particular for men and obese patients, with the objective of decreasing the risk of reoperation and the postoperative mortality rate.

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Vaginal endosonography of the anal sphincter complex is important in the assessment of faecal incontinence and perianal sepsis

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Background Anal endosonography is an established technique in the evaluation of anorectal disease.

However, it is sometimes difficult to visualize the anterior part of the sphincter complex and anal endosonography may be impossible when anal pain or stenosis is present. The aim of this study was to evaluate vaginal endosonography in the diagnosis of faecal incontinence and perianal sepsis.

Methods Anal and vaginal endosonography were performed in 56 women with faecal incontinence ($n = 36$) or perianal sepsis ($n = 20$). The technique and pelvic floor anatomy were described, anal sphincter measurements with anal and vaginal endosonography were compared, and the additive value of vaginal over anal endosonography in the diagnosis of faecal incontinence and perianal sepsis was assessed.

Results The pelvic floor was clearly imaged with vaginal endosonography. However, after a relatively short learning curve it was still not possible to image the anal sphincters in three of 28 patients.

Except for external anal sphincter thickness, which was significantly lower, all anal canal structure measurements were greater with vaginal than with anal endosonography. Concerning the diagnosis of either faecal incontinence or perianal sepsis, vaginal endosonography added important information in comparison with anal endosonography in 14 (25 per cent) of 56 patients.

Conclusion Vaginal endosonography provides reliable images of the anal sphincters in an undistorted fashion, thereby increasing the diagnostic yield of faecal incontinence and perianal sepsis in 25 per cent of patients. Therefore, endosonographers should become acquainted with this technique.

Anorectal endosonography has evolved rapidly in recent years and is now an established procedure in the staging of rectal carcinoma^{1,2}. Furthermore, it is used in the assessment of sphincter defects in faecal incontinence^{3–5} and of perianal abscesses and fistulous tracts^{6–8}. Although anal endosonography is generally well tolerated and easy to perform, it is not always possible to use this technique, for example when there is anal canal stenosis or anal pain⁹. Furthermore, the anal canal is distorted by the endoanal probe and it is sometimes difficult to visualize the anterior part of the sphincter complex¹⁰. For female patients there is an alternative: vaginal endosonography provides undistorted images of the anal sphincters¹¹ and may also produce better images of the anterior anal sphincter and anovaginal septum.

The aim of this study was to evaluate vaginal endosonography in patients with faecal incontinence and perianal sepsis. The technique and pelvic floor anatomy were described, anal sphincter measurements with anal and vaginal endosonography were compared, and the additive value of vaginal endosonography in the diagnosis of faecal incontinence and perianal sepsis was assessed.

Patients and methods

From October 1994 to August 1995, anal and vaginal endosonography were performed in a single session in 36 patients with faecal incontinence (mean age 50 (range 26–82) years) and in 20 with perianal sepsis (mean age 39 (range 26–69) years).

Indications for referral of perianal sepsis were suspected perianal fistula ($n = 11$), rectovaginal fistula ($n = 5$) and perianal abscess ($n = 4$). Eleven patients had histologically proven Crohn's disease.

Endosonography

Anal and vaginal endosonography were performed using a Diagnostic Ultrasound System (type 3535; Brüel and Kjær, Naerum, Denmark) with a 7-MHz rotating endoanal probe (type 1850, focal range 2–4.5 cm) covered by a water-filled hard sonoluculent cone (diameter 1.7 cm), producing a 360° view. The probe was first inserted into the vagina, until the rectum was visualized. It was then gradually withdrawn while images were made of the puborectalis muscle and anal sphincters. Subsequently the probe was introduced into the rectum and serial radial images of the puborectalis muscle and anal canal were taken. If possible, hydrogen peroxide enhancement was used in the assessment of fistulous tracts¹². Technical results were reviewed afterwards.

Pelvic floor anatomy and sphincter measurements

The structures of the pelvic floor visualized with vaginal endosonography were related to the known pelvic floor anatomy as described previously in dissected specimens and images obtained with anal endosonography¹⁰. Puborectalis muscle thickness (PMT), internal anal sphincter thickness (IST), external anal sphincter thickness (EST) and submucosal thickness (SMT) were assessed in 23 women with an electronic calliper (steps of 0.1 mm, accuracy 2 per cent of range) incorporated in the ultrasound scanner. PMT was assessed in three places (dorsal, left and right) and IST, EST and SMT in four (ventral, dorsal, left and right).

Diagnostic value

All anal and vaginal endosonographic findings were compared independently by two authors (A.C.P. and R.J.F.F.-B.), using

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anal endosonography as the 'gold standard' endosonographic technique. In cases of faecal incontinence, sphincter defects detected with anal endosonography and/or vaginal endosonography were recorded and correlated afterwards. In patients with perianal sepsis, the findings of anal and vaginal endosonography were compared for the presence of fistulous tracts, abscesses and sphincter defects.

The additive value of vaginal endosonography was defined as obtaining clearer images or more adequate and precise information than with anal endosonography. This included cases where it was impossible to perform anal endosonography because of pain or stenosis. Lack of correlation between anal and vaginal endosonography necessitated matching to surgical records or magnetic resonance imaging (MRI) when possible.

Statistical analysis

Mean(s.d.) values of PMT, SMT, IST and EST were calculated. Vaginal and anal measurements were compared with Student's *t* test and correlation was assessed with the Pearson correlation test.

Results

The anal sphincters were visualized clearly with vaginal endosonography in 43 (77 per cent) of 56 patients. In 13 women vaginal endosonography failed to image the sphincters, whereas anal endosonography imaged them clearly in all cases. The use of a balloon to avoid air artefacts did not improve transvaginal imaging in these cases. In part, the inadequate imaging was due to a learning curve: vaginal endosonography in ten of the first 28 patients was inadequate, whereas this was the case in only three of the subsequent 28. In these women, pelvic floor anatomy (especially a broad perineum) did not allow proper imaging of the anal sphincters. Another less significant problem which was frequently encountered was the difficulty in viewing the dorsolateral part of the external anal sphincter, the focal range of the transducer being a limiting factor.

Description of anatomy with vaginal endosonography

Fig. 1a shows the puborectal muscle and its insertion point at the os pubis, the fibrae prerectales of the levator ani and the perirectal fat, as well as the perivaginal fibrous tissue. The rectum with its submucosal folds was seen. Anterior to the vagina the urethra was imaged as a large echogenic structure surrounded by echolucent muscle tissue. Withdrawing the probe slowly, the external and internal anal sphincters were visualized (Fig. 1b). Within the internal anal sphincter complex lay the internal haemorrhoidal plexus. Anteriorly there was a demarcation between the external anal sphincter and perivaginal fibrous and transverse perineal muscle (not seen in all patients). In cases of obstetric trauma, scarring of the anovaginal septum with or without extension into the sphincter complex was easily detected with vaginal endosonography, being echolucent compared with the echogenic perivaginal fibrous tissue (Fig. 2).

Sphincter measurements

Except for the external anal sphincter, which was detected as significantly thinner (mean(s.d.) 5.7(1.8) versus 7.5(1.0) mm, $P < 0.001$), all anal canal structure measurements were significantly greater when determined by vaginal endosonography. Mean(s.d.) puborectal muscle thickness was 8.7(1.3) versus 7.6(1.0) mm ($P = 0.001$),

mean(s.d.) internal anal sphincter thickness was 2.9(1.0) versus 1.7(0.3) mm ($P < 0.001$) and mean(s.d.) submucosal thickness was 5.8(1.0) versus 2.4(0.5) mm ($P < 0.001$). All anal and vaginal endosonographic measurements showed a correlation: mean puborectal muscle thickness $r = 0.45$ ($P = 0.04$), external anal sphincter thickness $r = 0.64$ ($P = 0.002$), internal anal sphincter thickness $r = 0.52$ ($P = 0.016$) and submucosal thickness $r = 0.73$ ($P = 0.0002$).

Diagnostic value

Vaginal endosonography increased the diagnostic yield in 14 (25 per cent) of 56 patients: eight with faecal incontinence and six with perianal sepsis.

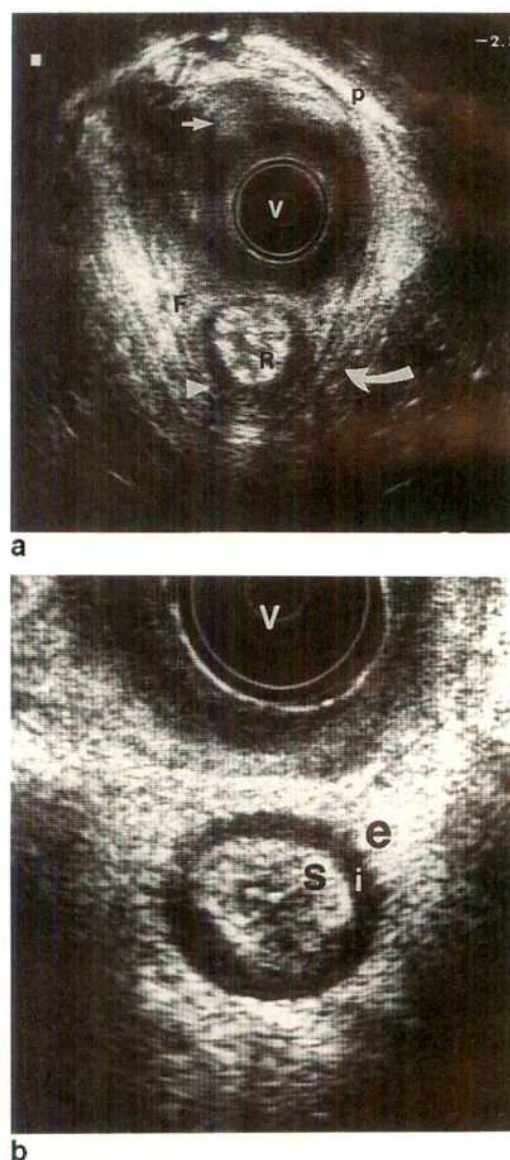


Fig. 1 a Normal pelvic floor anatomy with vaginal endosonography. The puborectal muscle (curved arrow), pubic bone (p), perirectal fat (white triangle), fibrae prerectales (F) and urethra (white arrow) are clearly visualized. v, Probe in the vagina; R, rectum. b Withdrawing the probe slowly, the external anal sphincter (e), internal anal sphincter (i) and the submucosa with the internal haemorrhoidal plexus (s) can be imaged

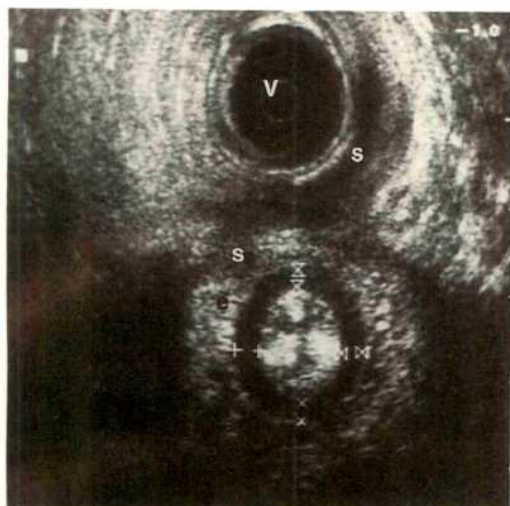
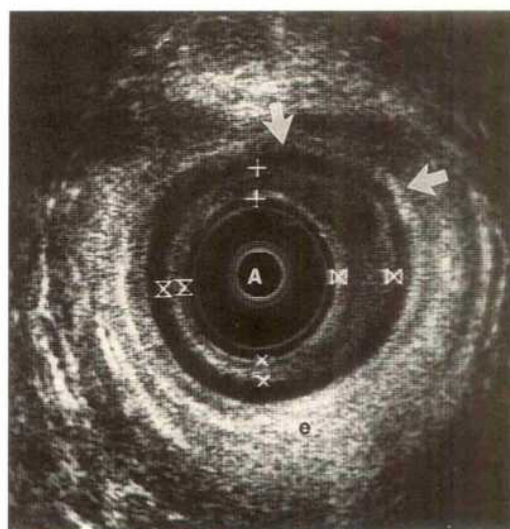


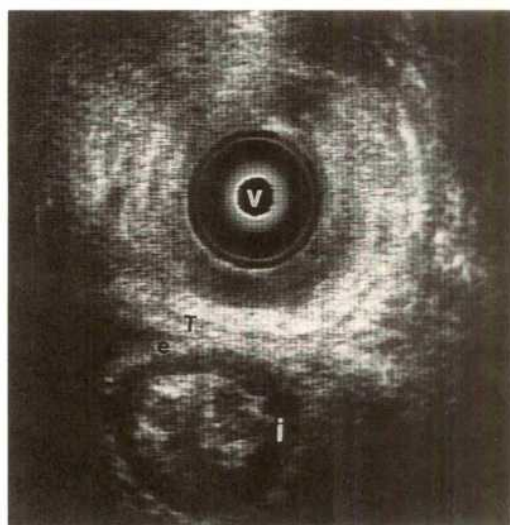
Fig. 2 Vaginal endosonographic image showing scarring (s) of the anovaginal septum due to obstetric trauma, extending into the external anal sphincter (e). The internal anal sphincter is intact. v, Probe in the vagina

Faecal incontinence. A defect of one or both anal sphincters was detected using anal endosonography in 27 of 36 patients. Of these 27 patients, the anal sphincters could not be imaged with vaginal endosonography in seven cases. Of the remaining 20 patients, vaginal endosonography demonstrated a sphincter defect in 16 cases. In the other four women no defect of the external anal sphincter was detected with vaginal endosonography (Fig. 3). In two of them the vaginal endosonographic findings were confirmed at operation. In the 16 cases in which a sphincter defect was seen with both anal and vaginal endosonography, a clearer image of the extent of the scarring of the anovaginal septum was obtained with vaginal endosonography in six patients. Vaginal endosonography therefore provided an important contribution to the diagnosis of faecal incontinence in eight of 36 cases. In six of these eight cases the contribution consisted of an improved anatomical definition of the sphincter defect. In the other two a sphincter defect, apparently demonstrated by anal endosonography, was excluded by vaginal endosonography, this being confirmed by surgery.

Perianal sepsis. In six of the 20 patients with perianal sepsis no pathology could be found at the time of the study. In the other 14 patients a perianal abscess ($n=2$), rectovaginal fistula ($n=3$) or perianal fistula ($n=9$, four with a secondary tract to the vagina) was found using anal endosonography. Vaginal endosonography added important information to the diagnosis of perianal sepsis in six of the 20 patients. In these six patients the abscess or fistula was located between the anus and vagina. In four of these cases a better image of the fistulous tract was obtained, and in two vaginal endosonography demonstrated the internal opening of the fistula (Fig. 4). In the fifth patient a rectovaginal fistula could be detected only with vaginal endosonography and was confirmed by MRI. In the sixth patient, with severe perianal Crohn's disease, vaginal endosonography was the only alternative because of painful anal canal stenosis. Five patients had an anterior external anal sphincter defect shown by anal endosonography. Vaginal endosonography correlated with anal



a



b

Fig. 3 a Anal endosonographic image of a 69-year-old woman with faecal incontinence. An external anal sphincter defect seems to be present between the arrows from 11 to 2 o'clock. The internal anal sphincter is intact. The electronic callipers for measurements are placed around the submucosa. e, External anal sphincter; A, probe in the anorectum. b Vaginal endosonography shows that the anovaginal septum is intact, which was confirmed during surgery. v, Probe in the vagina; T, transverse perineal muscle; i, internal anal sphincter

endosonography in three of these patients. In one woman, vaginal endosonography was unable to image the sphincter complex, and in another the sphincters were shown by vaginal endosonography to be intact, as was confirmed by surgery.

Discussion

This study has shown that vaginal endosonography is a reliable technique for providing images of the puborectal muscle and the anterolateral part of the anal sphincter complex in most women. The learning curve is relatively short, but even with experience of this technique unfortunately it is still not possible to image the anal sphincters in approximately 10 per cent of patients. In

these women, pelvic floor anatomy (especially a broad perineum) does not allow proper imaging of the anal sphincters transvaginally. Another drawback is that the dorsal part of the external anal sphincter cannot be seen in the majority of patients with the equipment used. The use of lower frequency ultrasound may improve the imaging quality of this part of the anal sphincter. However, this is of only minor clinical relevance, as the main purpose of performing vaginal endosonography should be to obtain more information about the anovaginal septum and perivaginal structures. As was demonstrated in this study, especially in this part of the pelvic floor, normal anatomical structures and abnormalities related to faecal incontinence and perianal sepsis

are visualized clearly with this technique and not always with anal endosonography.

Sphincter measurements assessed with anal and vaginal endosonography were not equal. The explanation for these differences is twofold. First, not stretching the anal canal during vaginal endosonography results in greater measurements. This effect is most prominent in the submucosal layer. Second, the sphincters are observed at different angles with vaginal and anal endosonography, as the anal and vaginal canals are not entirely parallel. The reason for lower measurements of the external anal sphincter with anal endosonography is probably the limited focal range of the 7-MHz probe.

Vaginal endosonography increased the diagnostic yield in 14 (25 per cent) of 56 patients with faecal incontinence or perianal sepsis. Its additive value was in all cases limited to abnormalities located in the anovaginal septum. Scar tissue of the anovaginal septum as a result of traumatic delivery could be followed from its point of origin to its extension in the anal sphincters in most cases. This added important information to the diagnosis of obstetric trauma of the anal sphincters, especially when there was doubt whether the abnormalities recorded with anal endosonography were due to an artefact. In both the incontinence and sepsis groups a total of 32 anterior sphincter defects was seen with anal endosonography. A relatively poor correlation between anal and vaginal endosonography was noticed. A defect of the external anal sphincter seen with anal endosonography could not be reproduced with vaginal endosonography in five women. In three of these patients this was confirmed at surgery. Therefore, anal endosonography might overestimate the presence of external anal sphincter defects in patients with faecal incontinence. Artefacts may be the result of stretching the sphincter complex, thus creating a 'shine-through' effect. Other possibilities are the presence of air in the vagina or fibres of the deep transverse perineal muscle, crossing the anterior part of the external anal sphincter and thus interfering with its endosonographic visibility¹⁰. Although these results may have to be confirmed in more patients undergoing surgery, the authors believe there is an indication for vaginal endosonography if doubt exists regarding the presence of a sphincter defect, in order to determine whether or not to perform surgery.

In addition, vaginal endosonography might contribute to a more accurate endosonographic assessment of complicated perianal fistulas. The involvement of endosonography in perianal sepsis is important, as fistulography and computed tomography are considered less reliable in the diagnosis of perianal sepsis^{13,14} and endosonography can serve as an easy and inexpensive alternative to MRI. With vaginal endosonography, the extension of a fistula in the rectovaginal septum and towards the vagina can be visualized more clearly. Furthermore, with anal endosonography the internal opening of fistulous tracts is recognized in only 11–30 per cent of cases^{6–8}. Vaginal endosonography does not obliterate the internal opening, thereby permitting the hydrogen peroxide to flow through the fistulous tract into the anus. This improves the recognition of the internal opening. Future studies must challenge the accuracy of combined vaginal and anal endosonography compared with other techniques in complicated anovaginal sepsis. For the detection of sphincter defects in patients who have undergone previous surgery for fistulous disease, vaginal endosonography is of less clinical relevance than

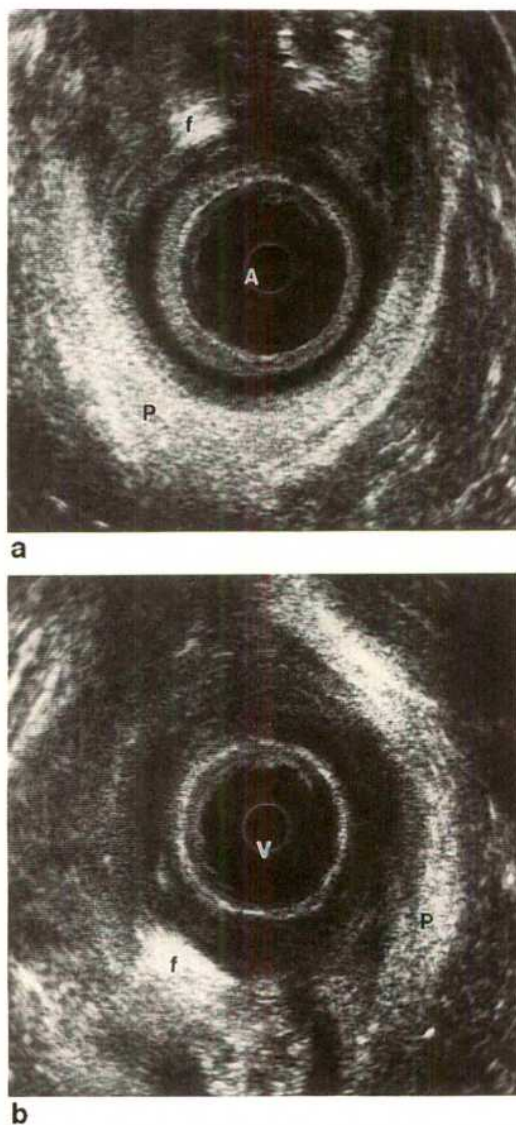


Fig. 4 a Anal endosonographic image of a 40-year-old woman with Crohn's disease, demonstrating a perianal fistula (f) at the level of the puborectal muscle (P). A, probe in the anorectum. Note that the fistula has an echogenic appearance because of the injection of hydrogen peroxide. The internal opening of the fistula is not clearly present at this level. b Vaginal endosonography, not obliterating the internal opening, reveals the site of the internal opening at the level of the puborectal muscle, just above the sphincter complex. v, Probe in the vagina

in faecal obstetric incontinence, as those defects can be located everywhere in the sphincter complex.

Finally, not disturbing the anatomy of the internal anal sphincter and submucosa may have potential benefits in diagnosing and understanding the pathophysiology of disorders in which these structures are supposed to play a role, such as anal fissures, proctalgia and haemorrhoids¹¹.

In conclusion, vaginal endosonography provides reliable images of the anal sphincters in an undistorted fashion. It increases the diagnostic yield in 25 per cent of investigations for faecal incontinence and perianal sepsis. It is important that those performing endosonography become acquainted with this technique. However, technical difficulties limit its use to cases in which there is doubt about the existence of obstetric injury and when assessing fistulous tracts located in the anovaginal septum.

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Management of symptomatic locoregional recurrence during regional chemotherapy for colorectal liver metastases

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Background The incidence of symptomatic locoregional recurrence is doubled in patients receiving regional chemotherapy with hepatic arterial floxuridine infusion (HAI) compared with that in those with colorectal liver metastases treated by symptom control. This study assessed the management of symptomatic locoregional recurrence in HAI-treated patients with colorectal liver metastases.

Methods A retrospective review of all patients with colorectal liver metastases treated by HAI in one hospital over a 10-year period was carried out and the management of those who developed symptomatic locoregional recurrence was studied.

Results Twenty-three (14 per cent) of 166 HAI-treated patients with colorectal liver metastases developed symptoms of locoregional recurrence. Liver metastases were responding to HAI at the onset of symptoms in 19 (ten abdominal, nine pelvic recurrence) of the 23 patients. Resection of abdominal recurrence was possible in seven of the ten patients, with a median hospital stay of 14 days; there was one perioperative death. Resected patients survived a median of 15 months after resection of the recurrence, with five of seven remaining free of symptoms of locoregional recurrence. In contrast, six of nine HAI-responding patients with pelvic recurrence treated by external beam radiotherapy died from uncontrolled symptomatic pelvic disease.

Conclusion Resection of abdominal recurrence achieved worthwhile palliation in patients with HAI-controlled liver metastases, but palliation of pelvic recurrence by irradiation was unsatisfactory.

Hepatic arterial floxuridine infusion (HAI) achieves a 50 per cent tumour partial response rate in patients with colorectal liver metastases¹, but the additional survival² resulting from liver metastasis control provides an opportunity for occult extrahepatic disease to become symptomatic. As a result, the incidence of symptomatic locoregional recurrence after HAI is twice that found in patients treated by symptom control³. Thus regional chemotherapy for colorectal liver metastases produces a novel management problem when a patient whose liver metastases are controlled by HAI develops symptoms from locoregional recurrence.

This paper assesses the management of symptomatic locoregional recurrence in patients receiving regional chemotherapy for colorectal liver metastases.

Patients and methods

All patients with colorectal liver metastasis treated by HAI between October 1986 and October 1996 were studied. HAI treatment criteria, floxuridine regimen and follow-up have been described previously². All patients underwent computed tomography (CT) of the liver at 4-month intervals during HAI treatment to monitor the response of liver metastases³. Abdominal and pelvic CT, intestinal barium contrast studies and endoscopy were undertaken as clinically indicated to diagnose locoregional recurrence when symptoms of extrahepatic

abdominal pain, alteration in bowel habit, intestinal bleeding or haematuria suggested that bowel or adjacent viscera might be involved with recurrent disease.

Patients developing locoregional recurrence in the presence of progressive liver disease despite HAI chemotherapy were treated by symptom-only palliation⁴. Those with extensive or multiple sites of abdominal recurrence whose liver metastases were responding to HAI received systemic 5-fluorouracil–folinic acid chemotherapy⁵. Symptomatic patients whose abdominal CT scan suggested localized and resectable locoregional recurrence, and whose liver metastases were responding to HAI, underwent second-look laparotomy with the aim of resecting abdominal disease, whereas those with intrapelvic recurrence were treated by pelvic irradiation and, where necessary, diverting colostomy.

Patients who developed disseminated disease during follow-up after treatment of locoregional recurrence received systemic 5-fluorouracil with folinic acid chemotherapy⁶.

Results

Patients

A total of 166 patients with colorectal liver metastases who received HAI chemotherapy were studied. Twenty-three (14 per cent) developed symptoms resulting in investigations that suggested locoregional recurrence (abdominal pain (five), anaemia (two), abdominal pain and vomiting, rectal bleeding, and haematuria). Liver metastases had not responded to HAI chemotherapy in four patients who were managed by symptom control and died from uncontrolled liver disease a median of 41 (interquartile range (i.q.r.) 23–67) days from detection of locoregional recurrence. In the remaining 19 patients, the median (i.q.r.) volume of liver metastasis had reduced by more than 50 per cent in response to HAI (109

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Table 1 Age, sex, and primary stage and site in patients receiving hepatic artery chemotherapy for colorectal liver metastases, by development of locoregional recurrence

	Locoregional recurrence (n = 23)	No locoregional recurrence (n = 143)
Median (i.q.r.) age (years)	54 (51–61)	59 (51–66)
Sex ratio (M:F)	1.5:1	1.4:1
Dukes stage (A and B:C)	1:5	1:4
Colon:rectum	1:1	2:1

i.q.r., Interquartile range

(44–374) ml before treatment *versus* 22 (8–177) ml after treatment) at the time when symptoms of locoregional recurrence developed. The remainder of this report considers these 19 patients. Patient details are shown in *Table 1* and sites of locoregional recurrence (ten abdominal, nine pelvic) in *Table 2*.

Abdominal recurrence

Resection of locoregional recurrence was possible in seven of the ten HAI-responding patients with intra-abdominal recurrence (sites of resection: right paracolic gutter, two; left paracolic gutter, ureter and iliac artery, one; small bowel and omentum, one; bladder dome, one; ovaries and omentum, one; upper rectum, one). The median volume of locoregional recurrence resected was 35 (range 2–1734) ml, and resection margins were clear of tumour on histological examination in all cases. Two of these patients also had recurrent pelvic disease which was not resected. Resection of abdominal disease was not undertaken in the remaining three patients who were found at laparotomy to have intra-abdominal dissemination. Median in-hospital stay for all patients undergoing second-look laparotomy was 14 (i.q.r. 11–17) days. One patient developed a postoperative syndrome including tachycardia, thrombocytopenia, liver and renal function abnormalities, which has been reported previously in patients with liver metastases⁶. This patient recovered with intensive supportive measures and subsequently survived for 470 days. There was one perioperative death (within 30 days of operation). This occurred in a patient with disseminated disease who underwent bypass of multiple areas of intra-abdominal recurrence and died from

pneumonia on the fourth postoperative day. The remaining eight patients made an uncomplicated recovery.

Pelvic recurrence

Recurrence developed within the true pelvis in nine HAI-responding patients (rectum, four; sacrum, three; perineum, one; vagina, one). In addition two patients underwent resection of abdominal recurrence and the formation of a diverting colostomy for concurrent pelvic disease. Treatment of all patients was by external beam irradiation, and also with brachytherapy in the patient with vaginal recurrence.

Survival

Median (i.q.r.) survival from the commencement of HAI treatment in the 143 patients who did not develop local recurrence was not significantly different from that of the 19 treated for symptomatic local recurrence (323 (183–543) *versus* 499 (328–611) days respectively, $P=0.193$, log rank test). Median (i.q.r.) survival from second-look surgery of all patients undergoing laparotomy for locoregional recurrence was 375 (260–463) days (443 (260–463) days in patients resected for recurrence, compared with 210 (107–246) days in those not resected). Median (i.q.r.) survival after completion of irradiation for pelvic recurrence was 150 (126–455) days. Median survival from second-look surgery or irradiation was significantly shorter ($P=0.04$, Mann–Whitney U test) in patients developing pelvic or pelvic plus abdominal recurrence than in those with abdominal recurrence alone.

Symptom palliation

Five of the seven patients having abdominal resection had no further abdominal symptoms and died from lung metastases. Recurrent abdominal symptoms developed in both patients who underwent abdominal resection in the presence of pelvic disease. Overall, only three of the nine patients with pelvic recurrence were free from symptoms of recurrence between radiotherapy and death.

Discussion

Liver metastases and locoregional recurrence are both more likely to develop in patients with biologically aggressive primary tumours⁶. Symptomatic local recurrences do not occur commonly in patients with untreated liver metastases because these patients first develop symptoms from uncontrolled growth of liver metastases⁷. However, when liver metastases are controlled by HAI, extrahepatic disease then develops in 70 per cent of patients². Where liver metastases had not responded to HAI, locoregional recurrence was managed by simple symptom control⁴. However, this comprised only four of the 23 HAI-treated patients who developed symptoms from locoregional recurrence. In most patients who developed locoregional recurrence, control of liver metastases produced additional survival, which necessitated control of locoregional recurrence.

Second-look laparotomy resulted in resection of abdominal recurrence in seven of ten patients undergoing laparotomy, and involved a median hospital stay of 14 days and perioperative death in one patient. The finding that patients who underwent excision of symptomatic abdominal recurrence survived a median of

Table 2 Site of locoregional recurrence in patients with liver metastases controlled by hepatic arterial chemotherapy

Site of locoregional recurrence	No of patients
Right paracolic gutter	2
Left paracolic gutter, ureter and iliac artery	1
Small bowel and omentum	1
Bladder dome	1
Ovaries and omentum	1
Rectum	5
Sacrum	3
Perineum	1
Vagina	1
Disseminated abdominal	3

15 months after recurrence resection, with the majority (five of seven) remaining free from symptoms of locoregional recurrence, suggests that this approach produced worthwhile palliation. Thus, suitably fit and motivated patients with HAI-controlled liver metastases who develop symptoms from localized and potentially resectable abdominal recurrence should be offered second-look laparotomy and resection. The one peri-operative death was in a patient with complete intestinal obstruction associated with multiple areas of intra-abdominal disease. This is in keeping with the previously reported poor results from bypass in patients with disseminated abdominal disease⁸, and suggests that operation is best avoided when complete bowel obstruction due to disseminated disease is diagnosed before operation.

Survival was significantly shorter in patients with pelvic recurrence than in those with abdominal recurrence in whom liver metastases were controlled by HAI, and six of nine patients with pelvic recurrence died from uncontrolled pelvic disease despite radiotherapy. It is possible that resection of pelvic recurrence might have produced better symptom control than irradiation. However, extensive surgical resection including sacral excision would be required to control pelvic local recurrence⁹, and the presence of intra-abdominal disease is a contraindication to this approach. As surgical resection of pelvic recurrence is inappropriate for palliation of patients with liver metastasis, and irradiation is ineffective, the best option for control of pelvic symptoms in patients with liver metastases may be to ensure optimal control of the primary tumour.

The larger proportion of primary tumours of the rectum in the locoregional compared with no locoregional recurrence population (Table 1) suggests that locoregional recurrence associated with HAI-treated liver metastases was more likely to occur with rectal than colonic carcinoma. Thus, where liver metastases are to be treated by HAI, patients undergoing treatment for an associated primary rectal carcinoma should undergo radical primary tumour excision¹⁰, if necessary with adjuvant primary tumour irradiation¹¹. Radical primary tumour excision can be undertaken safely¹² where the volume of liver metastasis is less than 1 litre (roughly 40 per cent liver replacement by metastases³). In addition, if the surgeon is appropriately experienced¹³, the hepatic artery can usually be cannulated at the same procedure^{2,14}, thereby sparing the patient an additional cannulation laparotomy before commencing HAI chemotherapy for liver metastasis.

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Intra-abdominal and pelvic abscess in Crohn's disease: results of non-invasive and surgical management

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Background Intra-abdominal and pelvic abscesses occur in 10–30 per cent of patients with Crohn's disease. The aim of this study was to establish the clinical characteristics and outcome of patients admitted over a 4-year period with an abdominal or pelvic abscess secondary to Crohn's disease.

Methods Patients with Crohn's disease-related intra-abdominal or pelvic abscess were identified from a prospectively collected database, comprising all admissions between 1991 and 1994. Medical records were reviewed retrospectively and data gathered regarding management and outcome.

Results Thirty-six patients were identified with Crohn's disease-related abscess, of whom 15 were considered for initial percutaneous drainage. Drainage was technically possible in eight of these patients: it failed in four, gave good long-term results in two, and was followed by recurrence after 3 years in one and by later surgery unrelated to the abscess in one. Twenty-eight patients underwent surgery, with only four requiring a stoma. Complications occurred in 12 patients. At 3 months, 22 of the 36 patients were in remission.

Conclusion Crohn's intra-abdominal abscesses are associated with a high morbidity rate. Selected cases can be drained percutaneously, without adding to the morbidity, and sometimes resulting in abscess resolution.

Intra-abdominal and pelvic abscesses occur in 10–30 per cent of patients with Crohn's disease at some time in the course of the illness^{1–3}. Up to 10 per cent of such abscesses are unsuspected clinically, but are diagnosed at laparotomy for disease unresponsive to medical therapy¹. This complication arises as a result of the transmural inflammation characteristic of Crohn's disease, with localized perforation resulting in an abscess cavity communicating with the bowel lumen. Management has traditionally been surgical but recent series have suggested that percutaneous drainage may have a role to play in the management of this disease. The clinical characteristics, management and outcome of patients with such abscesses, treated in a tertiary referral practice involving a multidisciplinary team of surgeons, physicians and radiologists, has been reviewed in this paper.

Patients and methods

Patients with Crohn's disease-related intra-abdominal or pelvic abscess were identified from a prospectively collected database, comprising all admissions between 1991 and 1994. Data were collected by the research records department and included underlying diagnosis, indication for admission, surgical procedures and outcome. Medical records were reviewed retrospectively. All patients had a diagnosis of Crohn's disease confirmed histologically according to standard criteria. The presence of an abscess was confirmed radiologically using a variable combination of ultrasonography, barium studies and computed tomography (CT). Patients with perianal sepsis were excluded unless they had concomitant intra-abdominal abscess. Patients with intra-abdominal or pelvic abscess developing within 3 months of surgery were also excluded.

Results

Presentation and diagnosis

A total of 531 patients with Crohn's disease were admitted 1156 times over the 4-year period. Of these, 36 patients (22 women; median age 35 (range 20–78) years) were admitted for management of Crohn's-related abscess. Follow-up from presentation with an abscess ranged from 3 months to 4 years (mean 18 months).

The median age of onset of Crohn's disease was 26 years and median duration of disease was 10 (range 1–40) years. Twenty-seven of the 36 patients had a past history of surgery for Crohn's disease, and 13 had previously had an operation for abscess or enterocutaneous fistula.

The abscess presented subacutely in 26 patients, with a history of ongoing active disease refractory to steroids. The remaining ten patients had an acute onset of symptoms with relatively sudden onset of abdominal pain and signs of sepsis. None of the patients had septicaemia at presentation.

An abdominal mass was present in 22 patients and an enterocutaneous fistula developed in nine. The fistula was spontaneous (i.e. with no past history of abdominal surgery) in two patients, both of whom had a relatively short history of Crohn's disease (2 years). Of the remaining seven patients with fistulas, four had a past history of enterocutaneous fistula or abscess. These results are comparable to those in a previously published series of patients with Crohn's disease-related enterocutaneous fistula⁴. Symptoms and signs of subacute bowel obstruction, including colicky abdominal pain and distension, vomiting and intermittent constipation, were present in six patients.

Review of therapy during the year preceding presentation revealed a history of steroid dependence, defined as a continuous requirement for steroids at a dose of more than 5 mg for more than 6 months, in 17 patients.

Table 1 Distribution of Crohn's disease in 36 patients with intra-abdominal abscess

	No. of patients
Extensive ileocolonic	14
Ileocaecal or anastomotic	12
Colonic disease only	5
Small bowel disease only	5

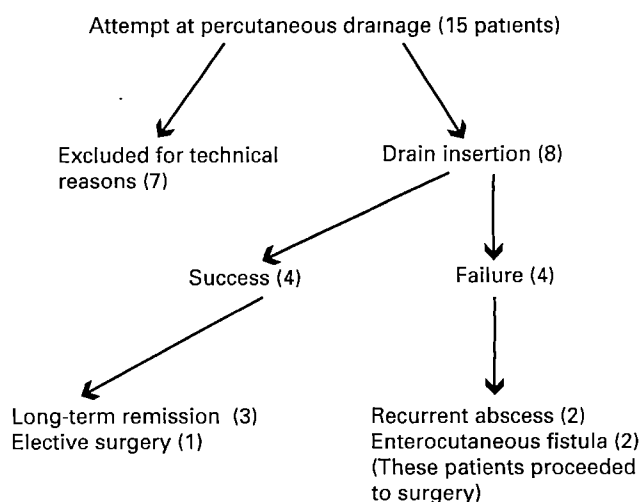
Six patients had recently started a course of steroids, and 12 were off steroids. Other therapeutic agents included 5-aminosalicylic acid derivatives in 12 patients; three were taking azathioprine. One patient each had received a course of cyclosporin and methotrexate, without significant benefit.

Distribution of disease in these patients with Crohn's disease-related abscesses is shown in Table 1. Radiological confirmation of the abscess cavity was by abdominal ultrasonography in 28 patients and CT in 13, with some patients having had both examinations. All the patients had barium or water-soluble contrast studies, including sinography in patients with an enterocutaneous fistula. A localized perforation of the bowel wall with bowel to abscess communication was demonstrated in 21 patients. These fistulas were shown to originate from a previous surgical anastomosis in 12 patients.

Management

Conservative management (Fig. 1). Eight patients were managed without laparotomy. Four of these had spontaneous percutaneous discharge of the abscess. Of these, three achieved prolonged remission with medical therapy, and one developed a chronic persistent low-output enterocutaneous fistula and required long-term enteral feeding via a percutaneous gastrostomy. Surgery was not undertaken in this patient owing to extensive past surgery for recurrent fistulas. Three other patients were drained percutaneously under imaging without the need for later surgery, and one patient had incision and drainage of abscess under general anaesthesia without subsequent definitive surgery. This patient continued to have a low-output enterocutaneous fistula 2 years later, requiring home parenteral nutrition. Operative management was avoided because of previous protracted postoperative complications.

Percutaneous drainage (Fig. 2). Percutaneous drainage was considered as an initial or definitive therapeutic option at presentation in 15 patients. However, the abscess cavity was deemed to be radiologically inaccessible or drainage inappropriate because of the complex multilocular nature of the abscess in seven patients. The remaining eight patients had a percutaneous drain

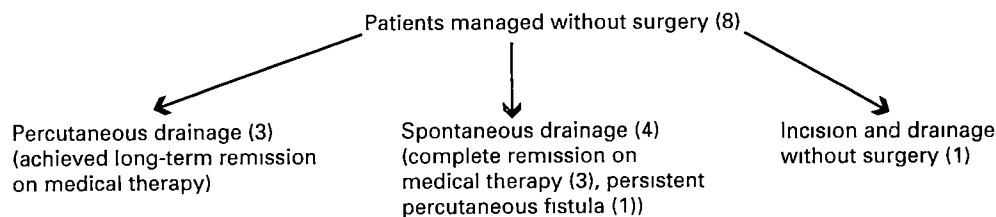
**Fig. 2** Outcome of patients undergoing percutaneous drainage of abscess

inserted successfully under ultrasonographic or computed tomographic guidance. In these patients the drain remained *in situ* for 2–4 weeks. These patients also received antibiotics, and steroids where this was considered appropriate.

Percutaneous drainage was successful in resolving the abscess in four patients. One of these patients had a demonstrable bowel to abscess communication, and two had ileopsoas abscesses, one of which was of a complex multilocular nature. One patient went on to elective resection of diseased bowel 6 months later, and remission was achieved in the remaining three without surgery. One of these three patients developed a recurrent retroperitoneal abscess after a 3-year asymptomatic period. As the patient was elderly and declined surgery, the abscess was again drained percutaneously, resulting on the second occasion in an ongoing low-output fistula.

The remaining four patients who underwent percutaneous drainage developed complications, with rapid abscess recurrence in two and a new enterocutaneous fistula at the site of drainage in the other two. These four patients all went on to have surgery. A further patient had percutaneous aspiration of the abscess on two occasions, without drain insertion, but abscess recurrence occurred on both occasions leading to surgery.

Surgery. Twenty-eight patients had *en bloc* resection of diseased bowel from which the abscess arose, drainage of the abscess cavity and antibiotic cover. Of these, four patients had had previous surgical abscess drainage and five had had percutaneous drainage. The remaining 19 patients underwent definitive surgery without previous

**Fig. 1** Outcome of patients managed without surgery

abscess drainage. A stoma was required in only four patients. At surgery the abscess was found to arise from the small bowel in 13 cases, from the colon in seven and from a previous surgical anastomosis in eight.

Psoas abscess. Of eight patients with psoas abscess, three underwent percutaneous ultrasonographically or CT-guided drainage of abscess. This resulted in long-term remission in two patients, although one of these developed a further abscess at the same site 3 years later. In the third patient, complex ongoing intra-abdominal sepsis required two subsequent operations; the sepsis was accompanied by a prolonged illness requiring parenteral nutrition, and complicated by multiple episodes of septicaemia culminating in tricuspid valve endocarditis. This patient underwent tricuspid valve replacement. The intra-abdominal sepsis was controlled eventually, although the patient is left with short bowel syndrome.

The abscess was not amenable to percutaneous drainage in five patients, all of whom underwent surgical drainage of the abscess and resection of diseased bowel as a single-stage operation with no covering stoma. Three of these patients had an uneventful postoperative recovery, but the other two developed postoperative complications with recurrent abscess in one and an enterocutaneous fistula in the other. Both were managed conservatively with percutaneous drainage of the abscess and subsequently made a full recovery

Associated morbidity and outcome (Fig. 3)

Minimum follow-up was 3 (mean 18) months after treatment. At 3 months, 22 of the 36 patients had achieved complete clinical remission. After follow-up of up to 4 years there were no deaths.

Twelve of the 28 patients treated surgically suffered major postoperative morbidity, with some having more than one complication (Table 2). These included abscess recurrence in nine patients, enterocutaneous fistula in four (including two new fistulas), bowel obstruction in three, wound infection in two, anastomotic leak in one, short bowel syndrome in six (of whom two required long-term parenteral nutrition) and septicaemia in three, including the patient who had recurrent intra-abdominal sepsis requiring prolonged parenteral nutrition leading to *Staphylococcus aureus* tricuspid valve endocarditis from

Table 2 Postoperative complications following surgery for abscess

	No of patients
Short term	
Abscess recurrence	9
Enterocutaneous fistula	4
Bowel obstruction	3
Wound infection	2
Anastomotic leak	1
Septicaemia	3
Tricuspid valve endocarditis	1
Further surgery	7
Long term	
Short bowel syndrome	6
Long-term home total parenteral nutrition	2

which he subsequently recovered. Complications were managed conservatively in five patients but the remaining seven required a further 11 operations. Six patients have developed short bowel syndrome with large fluid and electrolyte losses requiring parenteral replacement in two. Complications were found in eight of 17 patients in the steroid-dependent group, compared with six of 18 of those on short-term steroid (less than 1 month) or off steroids (*P* not significant).

Discussion

The transmural nature of the inflammatory process in Crohn's disease causes deep fissuring ulceration, which may result in complete perforation of the bowel wall. Fibrinous exudate on the serosal surface of the inflamed bowel results in adherence of adjacent bowel loops which frequently contain the perforation to form a localized walled-off abscess in the centre of an inflammatory mass. Free perforation in Crohn's disease is rare⁵. Abscesses in Crohn's disease occur most frequently between the leaves of the mesentery (intramesenteric), between adjacent bowel loops (interloop), between the bowel wall and adjacent viscera or the anterior abdominal wall (enteroparietal), and less frequently in the retroperitoneum or pelvis⁶. Fistulation to adjacent bowel or other viscera also occurs in these patients, with a perforating pattern of disease. There are few detailed series of outcome of this important complication of Crohn's disease in the literature.

Abscess formation in Crohn's disease is common, occurring in 17 per cent of one published series of 610 patients⁴. It carries high morbidity and mortality rates. The true incidence may well be higher, as a significant proportion of patients undergoing laparotomy for resection of unresponsive disease are found to have clinically unsuspected abscess formation. Presentation may include classical features with pyrexia, rigors and an abdominal mass, but these features are frequently masked by the walled-off nature of the infection or by steroid or other immunosuppressant therapy.

Abscesses in Crohn's disease arise most commonly from the ileocaecal region and present with a right iliac fossa mass. If the ileocaecal perforation tracks into the retroperitoneum, an ileopsoas abscess can result⁷⁻¹². This can occasionally compress the ureter and result in

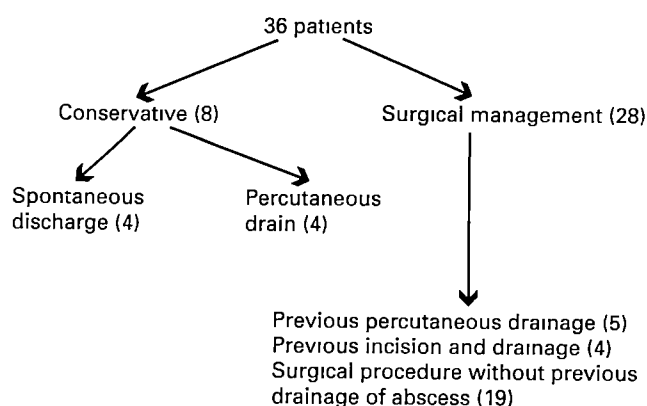


Fig. 3 Management outcome of 36 patients presenting with Crohn's disease-related abscess

hydronephrosis. The other common site for abscesses is in the left iliac fossa, arising from sigmoid disease or from an ileosigmoid fistula. Pelvic abscesses are also not infrequent and arise most commonly from terminal ileal or sigmoid disease. These may perforate into the bladder or vagina, resulting in an internal fistula. Similarly, enteroparietal abscesses may perforate on to the skin resulting in enterocutaneous fistulas.

The conventional therapeutic approach has involved a two-stage procedure with initial surgical incision and drainage followed by definitive surgery with resection of diseased bowel and fistula if present. In contrast, two retrospective studies have reported favourable outcomes following percutaneous drainage of Crohn's-related abscesses under ultrasonographic or computed tomographic guidance. Lambiase *et al.*¹³ reported permanent cure of the abscess in three patients following percutaneous drainage, none of whom had a demonstrable enteric communication to the abscess cavity. A further six patients in whom such a communication was demonstrable required definitive surgery within 7 weeks of drainage. Similarly, Safrit *et al.*¹⁴ described successful definitive cure of the abscess in two of seven patients with abscesses secondary to transmural bowel disease, the remainder requiring surgery. In the same series two postsurgical abscesses and five hepatic abscesses in patients with Crohn's disease were all treated successfully by percutaneous drainage.

In a prospective study by Casola *et al.*¹⁵, in which treatment was planned with the intent of using percutaneous drainage as the definitive therapeutic approach, results were more favourable. In this study 15 patients had successful abscess drainage percutaneously, with no complications including no enterocutaneous fistula. Eleven of the patients had spontaneous abscess formation and four presented in the immediate postoperative period with perianastomotic abscesses. Pre-existing enteroenteric and enterocutaneous fistulas closed in four of seven patients, and surgery was necessary only in three with enteric communication to the abscess cavity, although length of follow-up was not discussed. This surprisingly high success rate may be a function of the prospective nature of the study whereby percutaneous drainage was used with the intent of avoiding surgery if possible. This is also reflected in the somewhat longer duration of catheter drainage, which was between 8 days and 6 weeks.

The present retrospective review of the authors' experience of percutaneous drainage in the management of Crohn's disease-related abscesses showed that drainage was not considered in a large proportion of patients, partly as a result of established patterns of management. Where it was considered (15 patients), the abscess cavity was deemed to be inaccessible radiologically or drainage inappropriate owing to the complex multilocular nature of the abscess in seven patients. Of the remaining eight patients who had successful percutaneous drain insertion, surgery for abscess was avoided in four, although one patient required subsequent resection of active disease 6 months later. This success rate is comparable to that in the two previously reported retrospective studies mentioned above^{13,14}.

The postoperative abscess recurrence rate in the present series (nine of 28 patients) is comparable to that in previous reports of approximately 40 per cent^{16,17}. This high incidence of postoperative morbidity (12 of 28 patients), including short bowel syndrome in six, should encourage the increased use of a more conservative

approach where possible, particularly in patients with a past history of multiple resections and postoperative complications. Initial percutaneous abscess drainage has a beneficial temporizing effect in most patients, allowing control of sepsis and optimization of the patient's general condition and nutritional state. If or when surgery is subsequently required (to resect diseased, fistulating or stenosed bowel), the operation can be performed in an uninfected field and is likely to be significantly less complicated as a result, as well as allowing restoration of bowel continuity at the same operation.

However, abscess drainage needs to be combined with a willingness to delay surgery sufficiently to give time for the abscess to resolve and the track to heal. The drain should be kept *in situ* until dry, with frequent flushes to prevent blockage, and then withdrawn gradually, a few centimetres at a time, to allow the track to close. Antibiotics and nutritional supplementation may be necessary.

In conclusion, the present results demonstrate that despite the high morbidity rate associated with Crohn's disease-related abdominal abscess, these patients can be managed without mortality and with a satisfactory outcome in the majority of cases despite complex disease. An initially conservative approach with percutaneous drainage as a primary measure may reduce the need for surgery in selected cases, and enable bowel to be conserved in the long term. Further longitudinal prospective studies are required to assess the role of percutaneous ultrasonographically or CT-guided abscess drainage in these patients.

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Surgical resection of locally recurrent colorectal adenocarcinoma

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Background Recurrence rates after curative resection of colorectal adenocarcinoma remain steady at 50 per cent. Thirty per cent of the deaths are linked to locoregional recurrence. The aim of this study was to evaluate the results of resection for locoregional recurrence.

Methods This retrospective review analysed a series of 120 patients who underwent resection of colonic (56) or rectal (64) locoregional recurrence. Sixty-nine resections were considered as curative. Sixty-one recurrences required extended resection. There were nine synchronous hepatic resections.

Results The hospital mortality rate was 7 per cent and the morbidity rate was 40 per cent. The overall 5-year survival rate was 27 per cent. Survival was significantly higher: (1) after curative resection (44 *versus* 0 per cent after palliative resection, $P < 0.0001$); (2) in women (44 *versus* 11 per cent for men, $P = 0.0036$); and (3) after resection for intramural recurrence (45 *versus* 19 per cent for extramural recurrence, $P = 0.0024$). Multifactorial analysis showed that curability of the resection was the most important prognostic parameter.

Conclusion The results in this highly selected group seem to justify an attempt at resection whenever possible. Long-term results may be improved by using adjuvant treatment.

Recurrence rates after curative resection of colorectal adenocarcinoma have remained steady at 50 per cent for the past 30 years¹. These consist of hepatic metastases in 25 per cent of cases and abdominal or pelvic recurrence in 25–30 per cent^{2,3}; 30 per cent of deaths are linked to locoregional recurrence². More than 80 per cent of the recurrences appear in the first 2 years after resection and are diagnosed on presentation of symptoms in 75 per cent of cases^{4–6}. Local or locoregional recurrence is associated in 70–90 per cent of cases with peritoneal, metastatic or plurimetastatic evolution^{2,3,6}. The prevalence of isolated local recurrence is therefore low and patients who could benefit from curative resection are a highly selected group. The few studies on surgery for recurrence often include surgical resection and procedures for diversion or exploration^{6–9}. However, all aspects of local recurrence (natural history, prevention, treatment) make it a topical subject which has been reviewed recently¹⁰. The aim of this study was to evaluate the results of surgical resection for locoregional recurrence in a retrospective series of 120 patients.

Patients and methods

This retrospective study analysed a series of 120 patients (58 men and 62 women) from two centres who underwent operation for local recurrence of colorectal adenocarcinoma between 1975 and 1995. Local recurrence occurred a mean(s.d.) of 24.4(21) (range 2–114) months after primary surgery. Sixty-three per cent (76 of 120) of patients were treated elsewhere for the primary tumour.

Twenty patients were submitted to two resections and four underwent three resections. Patients having laparotomy and internal or external diverting procedures without resection were excluded. The mean(s.d.) age for patients with local recurrence was 62.7(10.4) (range 26–85) years. The primary tumour was colonic in 56 patients and was treated by segmental colectomy in

28 cases and hemicolectomy in 28. The primary tumour was rectal in 64 patients, treated by sphincter-saving resection (SSR) in 39 cases and abdominoperineal resection (APR) in ten; Hartmann's operation was performed in six patients, with a limited procedure in nine (eight transanal resections and one resection by the Kraske posterior approach).

For 19 referred cases (16 per cent) Dukes stage was not indicated; 12 patients had Dukes A tumours; 47 had Dukes B; 40 had Dukes C, and two had had a complete tumour response after preoperative irradiation of rectal cancer. The distribution of Dukes stage was identical for colonic and rectal cancers.

The distribution of local recurrence is shown in Table 1. Thirty-nine local recurrences (32 per cent) were asymptomatic. Only 14 of the 39 cases of asymptomatic local recurrence were diagnosed from levels of carcinoembryonic antigen (CEA). Twenty-six patients had associated metastases (17 hepatic, six pulmonary, three ovarian and one Troisier node) but local recurrence was predominant clinically.

The type of resection performed for the first local recurrence is shown in Table 2. Intramural local recurrences were resected by repeat colectomy or repeat SSR when possible. Perineal rectal resection was performed when intramural local recurrence was

Table 1 Locoregional recurrence of colorectal cancer: type of first recurrence according to site of primary tumour

	Colon (n = 56)	Rectum (n = 64)
Intramural recurrence (n = 31)		
Anastomotic recurrence (n = 25)	12	13
Recurrence after local resection (n = 6)	0	6
Extramural recurrence (n = 89)		
Perianastomotic recurrence (n = 74)	38	36
Pelvipерineal recurrence* (n = 9)	0	9
Distal recurrence† (n = 6)	6	0

*In the rectal tumour bed after abdominoperineal rectal resection; †recurrence located far from the initial resection site and/or the anastomosis (retroperitoneal fat, abdominal wall, mesentery)

Table 2 Locoregional recurrence of colorectal cancer: breakdown of operations for the first recurrence

Type of surgery	Total no	Extended operation
Repeated colectomy	31	17
Abdominoperineal resection	25	11
Anterior rectal resection	31	17
Hartmann procedure	10	4
Perineal rectal resection	6	
Total pelvic exenteration	4	4
Anterior pelvic exenteration	5	5
Local resection	3	
Colpohysterectomy	2	2
Abdominal wall resection	2	
Resection of small bowel	1	1
Total	120	61

located in the rectal stump after Hartmann's procedure. Extramural local recurrences often needed extended resection, and APR was usually performed for rectal perianastomotic local recurrence; pelviperineal local recurrence after APR was the most challenging recurrence to treat. If the local recurrence was fixed to the sacrum in the lower pelvis and not laterally, resection was extended to the sacrum. Forty patients had a colostomy after resection of the local recurrence and 13 further patients had a colostomy after the 24 repeat resections. Sixty-nine resections were considered as curative (58 per cent) and 51 as palliative, by surgical assessment. Sixty-one local recurrences (and 15 of the 24 repeat local recurrences) required extended resection of one or several contiguous viscera. There were nine synchronous hepatic resections.

Fifty-six patients received adjuvant treatment. 25 had irradiation before resection for rectal local recurrence, eight had peroperative irradiation in case of incomplete excision and 14 had postoperative radiotherapy; nine had postoperative chemotherapy alone.

The statistical methods used for this study were as follows: means were expressed with their standard deviation and compared with Student's *t* test; proportions were analysed with Pearson's χ^2 test or Fisher's exact test when theoretical numbers were insufficient. Survival was estimated between the date of resection of the first local recurrence and 30 October 1995. All deaths, including postoperative deaths, were related to the disease, because no systematic autopsy was performed. Only two patients were lost to follow-up at 21 and 33 months; survival rates were calculated using the Kaplan-Meier method and curves were compared with the log rank test. Results are presented with the 95 per cent confidence interval (c.i.). A Cox regression model was used to determine independent survival variables.

Results

Patient characteristics

The proportion of men was significantly higher than that of women in the rectal cancer group with local recurrence (37 of 58 men *versus* 27 of 62 women, $\chi^2 = 4.93$, 1 d.f., $P < 0.05$). The type of local recurrence was correlated with Dukes stage of the primary tumour, as 12 patients with Dukes A tumours presented seven intramural local recurrences, whereas the 47 patients with Dukes B tumours presented 35 extramural local recurrences and the 40 with Dukes C tumours presented 32 extramural local recurrences (stage A *versus* stages B and C, $\chi^2 = 6.34$, 2 d.f., $0.02 < P \leq 0.05$). Curability of the resection was significantly linked to the type of local recurrence (29 of 31 intramural *versus* 40 of 89 extramural recurrences, $\chi^2 = 22.23$, 1 d.f., $P < 0.0001$).

Mortality and morbidity

The hospital mortality rate was 7 per cent (eight of 120 patients). The mortality rate was not significantly influenced by the type of local recurrence (one of 31 anastomotic *versus* seven of 89 extramural recurrences, $\chi^2 = 0.22$, 1 d.f., $P = 0.7$), by the curative character of the resection (six of 51 palliative *versus* two of 69 curative resections, $\chi^2 = 2.42$, 1 d.f., $P = 0.08$) or by extending the resection (six of 61 extended *versus* two of 59 non-extended resections, $\chi^2 = 1.10$, 1 d.f., $P = 0.30$).

The immediate postoperative morbidity rate was 40 per cent (48 of 120 patients). Complications are reported in Table 3. Statistical analysis showed that morbidity did not depend on the type of recurrence (nine of 31 intramural *versus* 39 of 89 extramural recurrences, $\chi^2 = 2.09$, 1 d.f., $P = 0.15$) or type of resection (29 of 61 extended *versus* 19 of 59 non-extended resections, $\chi^2 = 2.93$, 1 d.f., $P = 0.08$). The mean (s.d.) duration of postoperative hospital stay was 30 (29) days. Repeated resection did not cause additional morbidity and mortality.

Survival

The overall 5-year survival rate was 27 (95 per cent c.i. 18–36) per cent and the survival rate without recurrence was 22 (95 per cent c.i. 14–30) per cent. Median survival was 24 months, 12 months after palliative resection and 53 months after curative resection. The 5-year survival rate was significantly higher: (1) after curative resection (44 (95 per cent c.i. 30–57) *versus* 0 per cent after palliative resection; $P < 0.0001$, log rank test) (Fig 1); (2) in women (44 (30–58) *versus* 11 (1–20) per cent in men, $P = 0.0036$); and (3) after resection for intramural local recurrence (45 (27–64) *versus* 19 (8–29) per cent for extramural local recurrence, $P = 0.0024$) (Fig 2). The 5-year survival rate was higher, but not significantly so: (1) after resection of colonic cancer local recurrence (39 (95 per cent c.i. 25–53) *versus* 16 (5–27) per cent for rectal cancer recurrence, $P = 0.204$); and (2) after non-extended resection (35 (21–48) *versus* 18 (6–30) per cent after

Table 3 Locoregional recurrence of colorectal cancer: complications following the first resection for recurrence in 48 patients

Complication	No of patients	Reoperation	Death
Multivisceral failure	4		4
Pleuropulmonary pathology	4		
Septicaemia	3		
Pyelonephritis	2		
Myocardial infarction	1		
Pulmonary embolism	1		1
Prolonged fever	1		1
Pelvic or perineal abscess	9	3	
Digestive fistula	8	4	
Parietal complications	5	1	
Intra-abdominal abscess	3	3	
Peroperative haemorrhage	3		2
Digestive haemorrhage	2	1	
Subocclusion	2		
Rectovaginal fistula	1		
Urinary fistula	1	1	
Urethral wound	1		
Total	51*	13	8

*Some patients had more than one complication

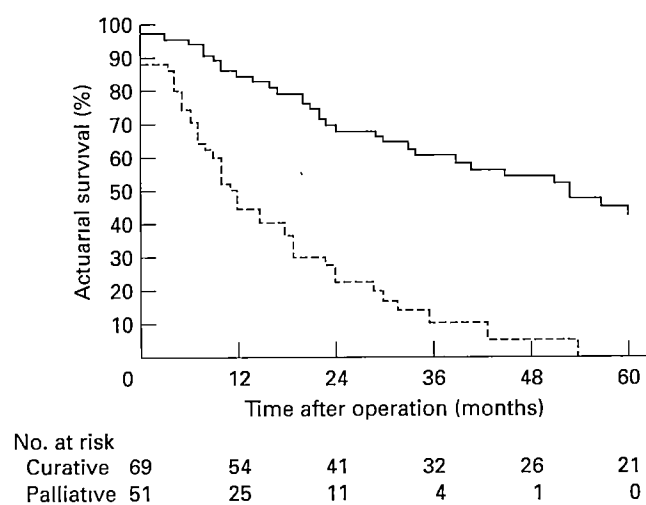


Fig. 1 Kaplan-Meier survival curves of patients undergoing curative (—) versus palliative (---) surgery. $P < 0.0001$ (log rank test)

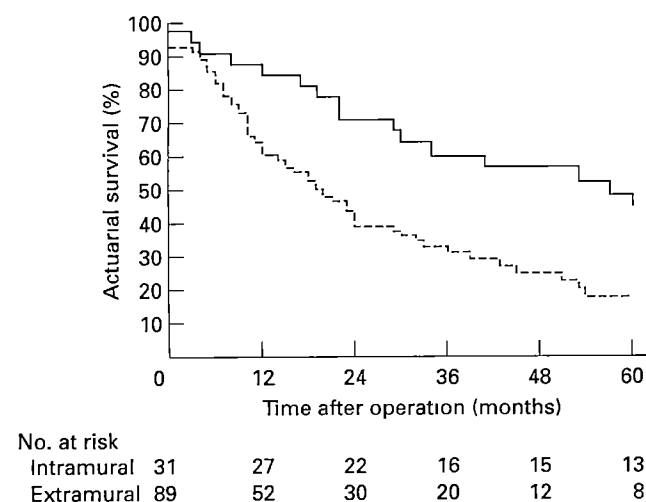


Fig. 2 Kaplan-Meier survival curves of patients with intramural (—) versus extramural (---) recurrence. $P = 0.0024$ (log rank test)

extended resection, $P = 0.053$). The 5-year survival rate was identical after resection of asymptomatic local recurrence (27 (95 per cent c.i. 11–44) versus 27 (16–38) per cent for symptomatic recurrence, $P = 0.38$). Moreover, survival was not significantly influenced by age under or over 40 years ($P = 0.65$), initial Dukes stage ($P = 0.48$), the time to local recurrence ($P = 0.25$), the existence of one or several 'histological' risk factors (no differentiation, peritumoral neoplastic embolism, invasion of perirectal fat, distal nodal involvement, invasion of neighbouring organs) during primary surgery ($P = 0.24$) or adjuvant treatment ($P = 0.24$). However, of the eight patients who received preoperative irradiation, prolonged local control was obtained in six.

The Cox regression model was used for the same variables. Two variables were significantly associated with survival: (1) curative resection ($P < 0.0001$) – there was a 3.9-fold increase in the risk of death for palliative resection (95 per cent c.i. 2.3–6.6); and (2) female sex, although at the limit of statistical significance ($P = 0.048$)

– there was a 1.7-fold increase in the risk of death for men (95 per cent c.i. 1.0–2.7). Median survival from the first resection for local recurrence in the 24 patients who had repeat resection was 47 months. Median survival after the last resection was 13 months. Median survival for the 26 patients with metastasis was 12 months, and three patients lived for 3 years or more.

Discussion

The resection rate for local recurrence has ranged from 25 to 75 per cent in surgical series published since 1980^{1,4,6–9,11–20}. The rates of curative resection for recurrence were from 0.2 to 2 per cent of cases in a study by Nelson²¹, who analysed the follow-up of eight series, each with approximately 1000 colorectal cancers. The aim of this work was to report on the surgical treatment of resectable local recurrence in a highly selected population. In this series there was a similar number of local recurrences from colonic and rectal cancer. Unless the rate of recurrence after colonic resection is lower than that after rectal resection²², the resection rate for colonic recurrence is higher than for rectal recurrence. The present results are comparable to those in most of the recent series with more than 20 patients^{1,4,6–9,14,20,23–25}.

In the literature, the operative mortality rate ranges from 0 to 16 per cent^{8,14}, comparable to that for primary surgery. The actuarial survival rate observed in the present series was 27 per cent at 5 years. Repeat resection enabled prolonged survival to be obtained. The value of palliative resection is debatable: only two patients survived for more than 3 years and median survival was 12 months. These values are comparable to the median survival reported for patients with unresected or unoperated local recurrence reported in surgical series^{3,6,7,14,19,23}. However, palliative resection can improve the quality of life¹⁴; in this series, almost 40 per cent of patients who had palliative resections remained ambulatory and asymptomatic for 6 months. Pelvipereineal recurrences are rarely resectable and have a very poor prognosis. Wanebo *et al.*²⁴, who advocate extended resection of pelvic local recurrence at the sacrum, observed a 15 per cent survival rate at 5 years when recurrence occurred after APR and 46 per cent when it occurred after SSR. Five of the nine patients of this type in the present series lived for between 2 and 3 years, and one patient lived for more than 3 years after two additional operations. The presence of resectable metastasis at the time of curative surgery for local recurrence did not influence survival in the series of Elias *et al.*⁸. In the present series, the median survival of such patients was 12 months. The improvement in results obtained by surgery could come from therapeutic associations and/or from earlier detection of recurrence.

Irradiation would seem to be a logical choice to reduce the prevalence of recurrence in the tumour bed, and its contribution to the treatment of local recurrence has been shown in two recent series^{8,9}. Preoperative irradiation could improve the rate of local control of the disease^{1,4,9,26,27}. This rate of local control could be doubled by chemotherapy used to improve radiosensitivity²⁸. There are no reported studies on the effectiveness of adjuvant chemotherapy after resection of local recurrence, but recent consensus established for high-risk colorectal primary tumours suggests that it is indicated theoretically^{29,30}.

The benefits of intensive follow-up after curative resection of colorectal adenocarcinoma are still under discussion^{21,31-33}. In the present series, 14 patients were explored on the basis of isolated levels of CEA, and the 5-year survival rate was no different after resection of asymptomatic local recurrence. A meta-analysis of papers that compare intensive follow-up with less frequent follow-up³⁴ has concluded that intensive follow-up with estimation of CEA levels for early detection of resectable recurrence improves the 5-year survival rate by 9 per cent. In a recent study, however, Moertel *et al.*³⁵ reported that monitoring CEA levels did not improve the rate of curative resection for recurrence.

In the present series, some recurrences could have been avoided by more adequate primary resection and/or adequate adjuvant therapy. However, the series was spread over several years and consensual treatment of primary tumours was not yet defined. Moreover, the surgeon's experience plays an important role in achieving good results after rectal surgery. A multicentre study by Phillips *et al.*³⁶ found that local recurrence rates differed significantly between surgeons (from 5 to 20 per cent). The proportion of men with local recurrence of rectal cancer in the present series was significantly higher than that for women, suggesting that the narrowness of the male pelvis increases the technical difficulty. For most patients there were no data on the adequacy of mesorectal excision during the first resection. The frequency of radial extension was often underestimated, and the efficiency of mesorectal excision has now been clearly demonstrated³⁷⁻⁴⁰.

In conclusion, the results in this highly selected group of 120 patients seem to justify an attempt at reresection whenever possible. However, long-term results in these cases could possibly be improved by using adjuvant treatment.

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Short note

Stapled haemorrhoidectomy: a feasible day-case procedure

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Milligan-Morgan haemorrhoidectomy is commonly performed in the UK but has failed to gain wide acceptance as a day-case procedure, largely owing to concerns about postoperative complications^{1,2}. This paper describes the preliminary evaluation of a new haemorrhoidectomy technique involving the use of gastrointestinal staplers.

Patients and methods

Thirty consecutive patients requiring haemorrhoidectomy for prolapsed haemorrhoids who were fit for day-case surgery were recruited. Preoperative preparation involved anorectal manometry and a 3-day course of lactulose 10 ml twice a day.

Under general anaesthetic, with the patient in the lithotomy position, rigid sigmoidoscopy was performed to exclude proximal disease in the lower sigmoid colon and rectum.

A Parks self-retaining retractor was positioned to expose each haemorrhoid and associated skin tag, which were grasped with tissue forceps and elevated away from the internal anal sphincter. The base was clamped between the forks of the stapler (Proximate Reloading Linear Cutter with safety lock-out 57-mm staple line; Ethicon, Edinburgh, UK) which was fired (*Fig 1*). Each staple line comprised two rows of staples and extended from the perianal skin to the mucosa of the anal canal. The excised haemorrhoid also had two corresponding rows of staples. The stapled skin was under-run with chromic catgut and excised, this was not an essential part of the operation but the staples remained for some weeks and caused mild discomfort in some patients. The anus was lightly packed with gauze soaked in 2 per cent lignocaine gel. The pack was removed 4 h later before the patient was discharged home with oral analgesics for moderate pain and lignocaine gel for local application, to be used as required. Two tablets of sennoside (senna) and 10 ml liquid paraffin and magnesium hydroxide emulsion were prescribed to be taken at night until the first bowel motion. The patients were reviewed weekly for 4 weeks and then at 3 and 6 months.

Results

There were 13 men and 17 women in the study with a median age of 41 (range 29–62) years. The mean duration of operation in 26 patients was 16 (range 9–22) min but in four patients the operating time was 27, 29, 30 and 33 min owing to large, confluent haemorrhoids and difficulty gaining access into the anal canal. In all other patients, the operation was easy to perform. Blood loss was minimal (10–12 ml) and the anal pack was removed without event in all. Pain was mild to moderate during the first 48 h in 28 patients but two patients required

overnight stay in hospital for pain control with parenteral analgesics. There was no case of urinary retention.

Wound healing was complete in 21 patients within 2 weeks, and within 3 weeks in a further seven; in two patients the wounds became infected and were allowed to heal by secondary intention.

At 6 months the staples could be palpated in the anal canal in four patients but there were no symptoms attributable to their presence, and all patients remained symptom free with no evidence of recurrent haemorrhoids, faecal incontinence or anal stricture. Repeat anorectal manometry was normal and histological examination did not reveal inclusion of internal sphincter muscle in the excised haemorrhoids in any patient. Three cartridges (one in the instrument and two reloads) were used in 26 patients, while four patients with large confluent haemorrhoids required four. The cost of a preloaded stapler was £153 and of a reloading cartridge £88.

Discussion

Stapled haemorrhoidectomy involves simultaneous excision of haemorrhoids and primary wound closure without dissection. The number of patients in this preliminary study is small and a controlled comparison with a conventional sutured technique has not yet been carried

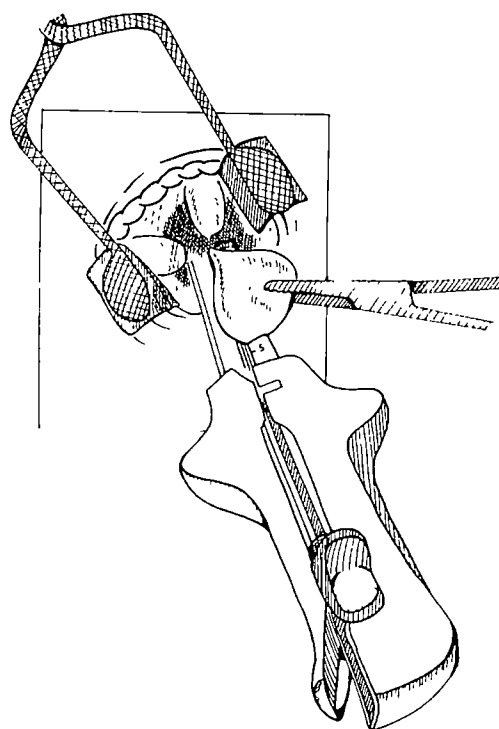


Fig. 1 Parks self-retaining retractor positioned to expose each haemorrhoid and tag, which are grasped by the stapling device before firing

out. Nevertheless, the apparent benefits of this procedure, especially rapid wound healing and satisfactory tolerance as a day-case procedure, justify further study.

The two main shortcomings of this technique were difficulty gaining access into the anal canal, particularly in those with large confluent haemorrhoids, and the cost of the stapling instruments. Access should be improved by a reduction in fork diameter and cost reduced without compromising results by use of a single row of haemostatic staples. A similar device, the Endo GIA 30 (AutoSuture, Ascot, UK) has a much smaller diameter but at the time of this study was more expensive. The cost of stapling may be further offset by savings from avoiding the use of inpatient beds³. Encouraged by these observed

benefits, the authors are conducting a randomized controlled comparison with the Ferguson (sutured) haemorrhoidectomy technique.

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TRISS methodology in trauma: the need for alternatives

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Background Trauma and Injury Severity Score (TRISS) methodology has become a standard tool for evaluating the performance of trauma centres and identifying cases for critical review. Recent work has identified several limitations and questioned the validity of the methodology in certain types of trauma.

Methods The usefulness and limitations of the TRISS methodology were evaluated in an urban trauma centre. Trauma registry data of 5445 patients with major trauma were analysed with respect to 30 demographic, prehospital, injury severity and hospitalization attributes. The performance of TRISS was measured primarily by the percentage of misclassifications, including false positives and false negatives, comparing the survival status predicted by TRISS with the true status. Sensitivity, specificity, and positive and negative predictive values were also measured for subgroups defined by the 30 attributes. Logistic regression analysis was used to identify significant independent factors related to the performance of TRISS.

Results The overall misclassification rate was 4.3 per cent. However, in many subgroups of patients with severe trauma the misclassification rate was very high: 34 per cent in patients older than 54 years with Injury Severity Score (ISS) greater than 20; 29 per cent in those with fall injuries and ISS above 20; 29 per cent in patients with injuries involving four or more body areas and ISS greater than 20; 28.6 per cent in patients with injuries needing admission to the intensive care unit (ICU) and ISS greater than 20; 26.4 per cent in patients in severe distress before reaching hospital with ISS greater than 20; and 26.1 per cent in patients whose ISS score was above 20 and who had complications in hospital.

Conclusion The TRISS methodology has major limitations in many subgroups of patients, especially in severe trauma. In its present form TRISS has no useful role in major urban trauma centres. Its use should be seriously reconsidered, if not abandoned.

With the introduction of organized trauma systems, the quality of trauma care came under intense scrutiny in most Western countries. The Trauma and Injury Severity Score (TRISS) methodology has become a standard tool for evaluating the performance of trauma centres and for identifying cases for critical discussion and areas for improvement. It is a recommendation of the American College of Surgeons Committee on Trauma to include the TRISS fallouts in the trauma quality improvement filters and subject them to critical review. Although there are some well known limitations of the TRISS methodology, it has remained the gold standard for comparing outcomes from different hospitals. The present study was undertaken to evaluate the usefulness and limitations of the TRISS method in a large urban trauma centre.

Patients and methods

Study setting and population

The study was conducted at the Los Angeles County and University of Southern California Medical Center. All deaths are initially reviewed by a minimum of six and up to nine trauma faculty at the weekly staff conferences and subsequently by the Combined Death Review Committee, which includes trauma surgeons, emergency physicians, neurosurgeons, the pathologist and the trauma nurse coordinator. The study covered calendar

years 1993 and 1994, and included only patients fulfilling one or more of the standard trauma registry criteria.

Data collection system

The trauma registry maintains a database which has over 130 data elements on each patient with trauma, including demographic characteristics, epidemiology, anatomical and physiological parameters of injury severity, clinical condition before and after arrival in the emergency department, procedures, hospital stay, survival and permanent disability status. The quality of data entry is checked on a quarterly basis by the Emergency Medical Services (EMS) of the Los Angeles County Department of Health Services. For the purpose of the present study, a trauma registry expert performed extensive human and computer checks for data completeness, accuracy and consistency. The Injury Severity Score (ISS) was calculated using the Abbreviated Injury Score (AIS) AIS-90. The Revised Trauma Score and the TRISS probability of survival (TPS) were calculated by standard methods.

Statistical analysis

The performance indicators used to measure TRISS usefulness and limitations included: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and misclassification rate of survival predicted by the TRISS method. Patients with a TPS of 0.50 or more were predicted to live and those with a TPS below 0.50 were predicted to die. Sensitivity of TRISS was defined as the number of patients correctly predicted to die as a percentage of the total number of patients who

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actually died; specificity of TRISS was calculated as the number of patients correctly predicted to live as a percentage of the total number of patients who actually lived; PPV was defined as the number of patients correctly predicted to die as a percentage of the total number of patients predicted to die; and NPV was defined as the number of patients correctly predicted to live as a percentage of the total number of patients predicted to live. It should be noted that the false-positive rate is $1 - \text{PPV}$ and the false-negative rate is $1 - \text{NPV}$. The misclassification rate was calculated as the sum of the number of patients who died but were predicted to live and the number of patients who lived but were predicted to die divided by the total number of patients.

The usefulness of TRISS to predict survival or death depends not only on its sensitivity and specificity, but also on the mortality rate in the population under consideration. This is because as the mortality rate decreases it becomes less likely that someone with a positive prediction of death will actually die, and more likely that the prediction represents a false positive. Thus the lower the mortality rate, the more specific a prediction must be to be clinically useful. The predicted values (PPV and NPV) which incorporate information on both the sensitivity and specificity of TRISS and the magnitude of the mortality rate are good measures of the clinical usefulness of TRISS. Consequently, the misclassification rate which incorporates both PPV and NPV is a good measure of the overall clinical usefulness of TRISS.

The performance of TRISS using these criteria was evaluated in subgroups defined by the following demographic and clinical characteristics of patients with major trauma: age, sex, ethnic group (Hispanic, white, black, and Asian), mode of transport (EMS *versus* non-EMS), prehospital respiratory assistance (endotracheal intubation or bag valve mask), severity of distress before reaching hospital, mechanism of injury (blunt *versus* penetrating), involvement of head, Glasgow Coma Score (GCS), haemodynamic status on admission (systolic blood pressure 90 mmHg or less), type of injury (including gunshot wound, stab wound, motorvehicle accident, motorcycle accident, pedestrian involvement and fall), ISS score, AIS score, regions of injury, hospital complications, surgical procedures and admission in the intensive care unit (ICU). A total of 30 attributes were analysed.

Attributes defining subgroups with twice the overall misclassification rate were chosen for logistic regression analysis by means of which the adjusted odds ratios of misclassification and their 95 per cent confidence intervals were derived. A stepwise logistic regression analysis was also performed on attributes which had P values of less than 0.25 for the comparison of misclassification rate among subgroups. Based on this analysis, the factors that contributed significantly to the misclassification rate were identified and compared with other findings.

Results

A total of 5713 patients with major trauma were admitted to this centre in 1993 and 1994. Of those admitted, 5445 (95.3 per cent) had complete information on survival status and TPS. The overall survival rate was 91.2 per cent and the mean TPS was 93.4 per cent. The Z statistics for 1993 and 1994 were -3.1 and -5.9 respectively and the M statistic was 0.96 for both years. The multidisciplinary peer review of deaths showed that four deaths (0.8 per cent) were preventable.

All patients with trauma

Tables 1–3 present the performance of TRISS for subgroups defined by demographic, prehospital, injury severity and hospital attributes. The P values testing the differences of misclassification rate between subgroups for each attribute are included.

The overall percentage of misclassification was 4.3 per cent, with a false-positive rate of 7.7 per cent and false-negative rate of 4.1 per cent. The subgroups with a misclassification rate greater than twice that of the overall rate included patients with the following characteristics: ISS greater than 20 (misclassification rate 21.1 per cent), injuries to four or more body areas (21.1 per cent), prehospital respiratory support (20.6 per cent), head AIS 4 or greater (18.3 per cent), abdomen AIS 4 or greater (18.3 per cent), GCS 12 or less (16.9 per cent), severe distress before reaching hospital (14.4 per cent); need for ICU admission directly from the emergency room or operating room (13.7 per cent), systolic blood pressure on admission 90 mmHg or less (13.1 per cent), chest AIS 4 or more (12.6 per cent), and age 55 years or more (10.8 per cent).

Thirteen attributes were found to fulfill the criteria stated above and were subjected to logistic regression analysis in which adjusted odds ratios of misclassification were derived. A total of 5284 cases with complete information on all 13 variables were used in the analysis. After adjusting for other factors in the analysis, the following attributes had significantly higher adjusted odds ratios: complications (odds ratio 10.93, $P=0.0001$), prehospital severe distress (odds ratio 4.74, $P=0.0001$), need for ICU admission (odds ratio 3.61, $P=0.0001$), age above 55 years (odds ratio 3.42, $P=0.0001$), ISS greater than 20 (odds ratio 1.83, $P=0.0019$) and maximum AIS 4 or more (odds ratio 2.61, $P=0.0238$).

The stepwise logistic regression analysis, in which variables with P values of less than 0.25 were included, identified seven subgroups that had contributed significantly to the misclassification. A total of 4982 cases with complete data on all variables were used in the multivariate analysis. In ranking order, they were: complications, severe distress before reaching hospital, need for admission to the ICU, maximum AIS 4 or higher, age 55 years or older, ISS greater than 20, chest AIS 4 or higher, and falls. With the exception of falls, the subgroups were the same as in the logistic regression analysis in which the 13 selected attributes were studied.

Patients with major trauma and Injury Severity Score greater than 20

The misclassification rate of TRISS was further examined among patients whose ISS was greater than 20 with respect to other attributes in the study. Fig. 1 displays a comparison of the misclassification rates of these attributes among patients with ISS greater than 20 with the rates for all patients with trauma. Subgroups of patients with the combination of ISS above 20 and hospital complications, severe distress before reaching hospital, ICU admission, age above 55 years, systolic blood pressure less than 90 mmHg, GCS 12 or less, head AIS 4 or greater, or chest AIS 4 or more, had significantly higher misclassification rates. The misclassification rate for patients aged 55 years or older with ISS greater than 20 was as high as 34 per cent, followed by 29 per cent for those with involvement of four or more body regions, 28.6 per cent for those needing admission to the ICU, 26.4 per cent for those with severe distress before reaching hospital, 26.1 per cent for those with complications, 25.8 per cent for those with head AIS 4 or more and 24.7 per cent for those with GCS 12 or less.

Table 1 Performance of Trauma and Injury Severity Score by injury severity attributes

Attribute	No. of patients	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Misclassification	
						Rate (%)	P
Glasgow Coma Score							
≤12	782	70.2	94.9	92.6	77.8	16.9 (14.3–19.5)	<0.001
>12	4663	2.9	99.98	75.0	97.8	2.2 (1.8–2.6)	
Systolic blood pressure (mmHg)							
≤90	601	77.1	95.3	93.5	82.7	13.1 (10.4–15.8)	<0.001
>90	4844	24.4	99.8	87.3	96.9	3.2 (2.7–3.7)	
Maximum AIS score							
1	2116	62.3	99.95	98.0	98.6	1.4 (0.9–1.9)	<0.001
2	1086	50.0	99.6	78.9	98.6	1.7 (0.9–2.5)	
3	1433	41.8	99.4	80.5	96.7	3.8 (2.8–4.8)	
4+	758	58.2	98.1	94.9	79.6	16.9 (14.2–19.6)	
No. of body regions involved							
1	3093	61.3	99.7	94.4	97.1	3.0 (2.4–3.6)	<0.001
2	1686	50.0	99.6	91.9	95.8	4.4 (3.4–5.4)	
3	500	53.4	98.8	88.6	92.5	7.8 (5.4–10.2)	
4+	114	47.5	95.0	86.4	77.2	21.1 (13.6–28.6)	
Head AIS							
<4	4969	57.6	99.6	90.2	97.3	3.0 (2.5–3.5)	<0.001
≥4	476	51.4	99.0	96.7	78.1	18.3 (14.8–21.8)	
Chest AIS							
<4	5294	49.1	99.7	92.3	96.1	4.1 (3.6–4.6)	<0.001
≥4	151	84.5	91.0	92.2	82.4	12.6 (7.3–17.9)	
Abdomen AIS							
<4	5314	56.3	99.6	92.1	96.2	4.0 (3.5–4.5)	<0.001
≥4	131	45.2	98.9	95.0	79.3	18.3 (11.7–24.9)	
Injury Severity Score							
≤15	4229	58.6	99.9	95.1	99.0	1.0 (0.7–1.3)	<0.001
16–20	563	24.6	99.2	80.0	91.0	9.4 (7.0–11.8)	
21–25	263	55.0	95.7	88.7	77.6	19.8 (15.0–24.6)	
26–30	201	53.0	97.5	93.6	74.7	20.9 (15.3–26.5)	
>30	189	70.0	91.5	94.8	58.1	23.3 (17.3–29.3)	
Injury Severity Score							
≤20	4792	45.1	99.8	91.4	98.1	2.0 (1.6–2.4)	<0.001
>20	653	60.7	95.6	92.7	72.5	21.1 (18.0–24.2)	

Values in parentheses are 95 per cent confidence intervals. AIS, Abbreviated Injury Score. *P values are for testing differences in misclassification rates among subgroups for each attribute. For maximum AIS score, number of body regions and injury severity score, P value indicates a significant increasing trend.

Table 2 Performance of Trauma and Injury Severity Score by hospitalization attributes

Attribute	No. of patients	Actual survival probability	TRISS survival probability	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Misclassification	
								Rate (%)	P
Hospital complications									
Yes	1414	0.68	0.80	54.9	98.1	93.1	82.7	15.4 (13.5–17.3)	<0.001
No	4031	0.99	0.98	61.8	99.9	84.0	99.7	0.4 (0.2–0.6)	
Surgery									
Yes	2066	0.90	0.94	31.0	99.0	77.5	93.1	7.6 (6.5–8.7)	<0.001
No	3379	0.91	0.93	72.9	99.9	98.1	97.6	2.3 (1.8–2.8)	
ICU admission									
Yes	1407	0.80	0.88	36.8	98.1	82.6	86.6	13.7 (11.9–15.5)	<0.001
No	4038	0.95	0.95	80.0	99.97	99.4	98.9	1.0 (0.7–1.3)	

Values in parentheses are 95 per cent confidence intervals. TRISS, Trauma and Injury Severity Score; ICU, intensive care unit. *P values are for testing differences in misclassification rates among subgroups for each attribute.

Misclassification rates by mechanism of injury

The overall misclassification rate for gunshot wounds was 4.9 per cent but for gunshot wounds in patients with ISS greater than 20 the misclassification rate was 17.3 per cent ($P < 0.01$). The respective figures overall and for those with ISS greater than 20 were 1.3 and 13.0 per cent for stab wounds, 3.8 and 19.6 per cent for motorvehicle accidents, 5.9 and 27.3 per cent for motorcycle accidents, 4.7 and 26.7 per cent for pedestrian accidents, and 5.8 and 29.4 per cent for falls. Stab wounds were found to have a significantly lower misclassification rate than gunshot wounds (1.3 *versus* 4.9 per cent, $P < 0.001$).

Discussion

Quality improvement is an inseparable component of any trauma system and outcomes have been under constant scrutiny by health professionals and health organizations.

The quality of trauma care was first evaluated by means of peer review of deaths and complications. Although philosophically it is difficult to imagine predicting life or death with a mathematical formula, it was felt that an objective and reproducible method was needed to measure outcomes and compare results from different trauma centres. The TRISS methodology was developed by Champion and Sacco in the 1980s to address these issues. Since then it has become a standard component of the quality improvement process in most trauma centres and is presently used for identification of deaths for review and for comparison of trauma outcomes from various centres. There was even discussion about using the TRISS methodology for purposes of trauma centre designation¹.

Subsequent studies identified several limitations of TRISS. In 1991, Cayten *et al.*¹ identified three limitations of the method: inability of TRISS to account for multiple severe injuries to a single body part, inability to predict

Table 3 Trauma and Injury Severity Score misclassification rate for selected attributes among patients with an Injury Severity Score above 20

Attribute	No. of patients	Percentage misclassified	Relative misclassification rate*	P*
Total no. of patients with ISS > 20	653	21.1		
Hospital complications				
Yes	475	26.1	3.30	<0.0001
No	178	7.9		
Prehospital severe distress				
Yes	451	26.4	2.78	<0.0001
No	199	9.5		
ICU admission				
Yes	427	28.6	4.03	<0.0001
No	226	7.1		
Age ≥ 55 years				
Yes	55	34	1.73	0.018
No	598	19.9		
Maximum AIS ≥ 4				
Yes	453	21.2	1.05	0.854
No	198	20.1		
4+ body regions				
Yes	76	29	1.46	0.092
No	575	19.8		
Prehospital respiratory support				
Yes	248	21.8	1.06	0.844
No	391	20.5		
Systolic blood pressure ≤ 90 mmHg				
Yes	236	16.5	0.70	0.039
No	417	23.7		
Glasgow Coma Score ≤ 12				
Yes	364	24.7	1.49	0.015
No	289	16.6		
Abdomen AIS ≥ 4				
Yes	81	18	0.86	0.636
No	572	21.5		
Head AIS ≥ 4				
Yes	267	25.8	1.44	0.020
No	386	17.9		
Chest AIS ≥ 4				
Yes	122	13.1	0.57	0.022
No	531	23		
Fall				
Yes	51	29	1.44	0.182
No	602	20.4		

ICU, intensive care unit; AIS, Abbreviated Injury Score. *Relative misclassification rate between those who had the attribute *versus* those who did not

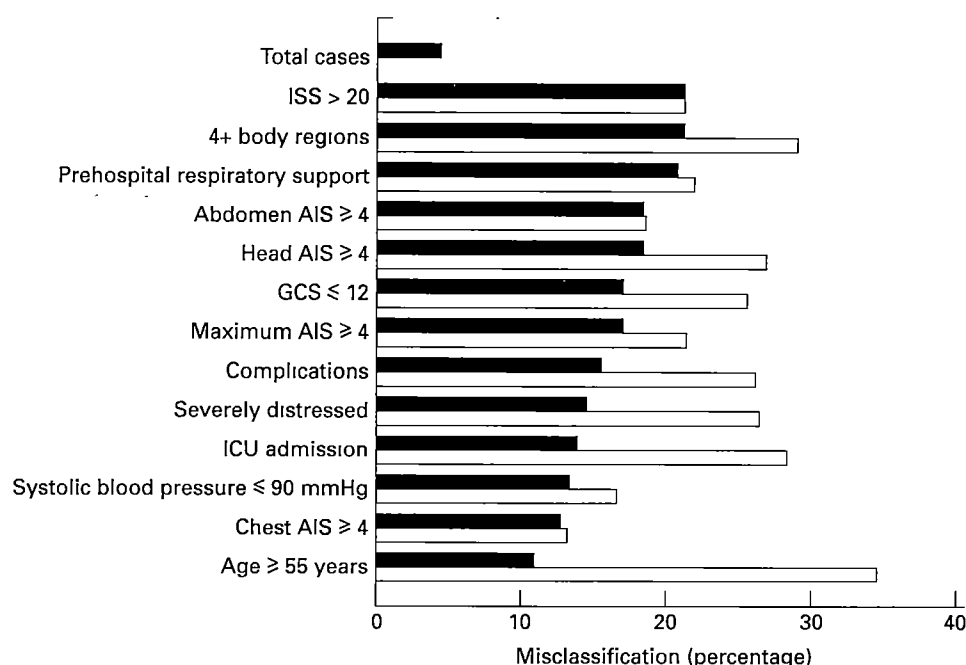


Fig. 1 Percentage misclassification of survival by Trauma and Injury Severity Score method among patients with injury severity score (ISS) greater than 20 ($n = 653$; □) compared with that for all patients ($n = 5445$; ■). AIS, Abbreviated Injury Score; GCS, Glasgow Coma Score; ICU, intensive care unit

survival in low falls, and the lack of distinction between gunshot wounds and knife injuries. The authors suggested that the method is not appropriate for making inter-hospital comparisons. They stressed that Z scores for a hospital with a high proportion of patients with gunshot wounds will probably compare unfavourably with Z scores for a hospital with a higher percentage of patients with stab wounds. Another study by Karmy-Jones *et al*² compared TRISS-designated unexpected outcomes with the findings of a structured peer review of the same cases. The peer review disagreed with 54 per cent of TRISS outcomes. In the present study, for the first time many other major TRISS limitations have been identified: ISS higher than 20, injuries to four or more body areas, the need for prehospital respiratory support, AIS 4 or more, the need for direct ICU admission, shock on admission and age 55 years or more. Overall, TRISS performed poorly in all severe injuries.

Despite the previously reported limitations, the overall performance of TRISS seemed acceptable. Most series reported a misclassification rate of only about 3 per cent³⁻⁵. In the present study the overall rate of misclassification was 4.3 per cent, which would give an impression of good TRISS performance. However, this low percentage of misclassification is related to the fact that the majority of these patients were of low risk. Of the total population, 93 per cent were under 55 years of age; 80 per cent did not sustain head injuries; 88.0 per cent had an ISS under 20; 97.9 per cent had trauma involving less than four regions; 85.6 per cent had a GCS of more than 12; 75 per cent were not severely distressed; 88.9 per cent were not in shock; 74.0 per cent had no complications and 74.1 per cent did not stay in the ICU. As a result the overall rate of misclassification was weighted down by the majority of low-risk cases.

The present study showed that TRISS performed well in predicting survival among the mildly injured patients but not for the moderately and severely injured patients.

Groups that had double the overall misclassification rate included patients with ISS greater than 20, multiple region involvement, prehospital respiratory assistance, head AIS 4 or higher, abdomen AIS 4 or higher, GCS 12 or lower, maximum AIS 4 or higher, hospital complications, severe distress before reaching hospital, admission to ICU, shock, chest AIS 4 or higher, and age 55 years or older.

The TRISS methodology is an expensive and labour-intensive process from which significant benefits should accrue. In the present study the TRISS was found to be inaccurate in many groups of patients, especially in those with severe trauma. In some categories of patients the misclassification rate was higher than 25 per cent. They were patients whose ISS was higher than 20 combined with any one of these conditions: older age (55 years or more), fall injury, injury involving four or more body regions, need for ICU admission, severe distress before reaching hospital, hospital complications or head AIS equal to or greater than 4 motorcycle and pedestrian accidents.

It is obvious that using TRISS without proper adjustment for case severity to make interhospital comparisons can be dangerous and misleading. Hospitals admitting large numbers of severe trauma cases probably compare unfavourably with hospitals admitting a lower percentage of patients with severe trauma. It has also been suggested that TRISS is a good way to select deaths for critical review. We believe that all deaths should be reviewed because it is not time consuming as supported by some TRISS advocates and useful trends may be identified. In addition, it has been shown in this study and other reports that there is poor correlation between TRISS and a structured peer review^{2,6}.

In conclusion, although trauma registries are extremely important in trauma systems, these data indicate that the TRISS methodology in its present form is an expensive and labour-intensive exercise with major limitations and

minimal benefits. It is time to reconsider its role and perhaps abandon it.

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Continuous antibiotic treatment for experimental abdominal sepsis: effects on organ inflammatory cytokine expression and neutrophil sequestration

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Background Tumour necrosis factor (TNF) α and interleukin (IL) 1β are produced in the lung after peritonitis and may contribute to neutrophil-mediated organ injury. It was hypothesized that, during experimental peritonitis, continuous rather than intermittent antibiotic therapy would reduce lung expression of TNF- α and IL- 1β messenger RNA (mRNA) and neutrophil sequestration.

Methods After caecal ligation and puncture, mice received either intermittent or continuous cefoxitin, or continuous metronidazole or aztreonam. Cytokine mRNAs were determined by reverse transcription differential polymerase chain reaction and lung neutrophil content by myeloperoxidase (MPO) assay.

Results Continuous cefoxitin reduced median (interquartile range (i.q.r.)) lung IL- 1β mRNA expression ((ratio to β -actin): continuous 0.18 (0.14–0.34), intermittent 0.46 (0.44–0.49), saline 0.43 (0.38–0.53), $P < 0.05$) and median (i.q.r.) lung MPO content (continuous 22.5 (9.7–40), intermittent 65 (57.5–76), saline 47 (41–64), $P < 0.05$) compared with intermittent therapy and saline controls. Continuous infusion was also associated with reduced bacteraemia ($P < 0.05$) but not serum TNF- α or endotoxin levels. Both continuous metronidazole and aztreonam reduced lung MPO concentration ($P < 0.05$) and TNF- α and IL- 1β mRNA expression ($P < 0.05$) compared with those in saline controls. These effects were dependent on a reduction in the number of susceptible bacteria rather than serum TNF- α or endotoxin levels.

Conclusion The stimulus for organ inflammatory cytokine production and neutrophil sequestration during peritonitis is the level of bacteraemia present, which is more effectively controlled with continuous antibiotic therapy.

Abdominal sepsis remains a leading cause of multiple organ failure (MOF) and the current mortality rate from MOF in patients with abdominal sepsis has not improved from 47 per cent over the past 10 years¹. There is thus a real need for new anti-infective therapies or modification of existing ones.

One potential modification could be to alter the course of antibiotic administration. Animal and clinical sepsis studies have reported that continuous infusion of antibiotics improves survival compared with intermittent dosing^{2–4}. In general, the benefits of continuous infusion have been seen in immunosuppressed models or patients. However, a positive effect on survival in a clinically relevant model of a Gram-negative surgical infection using a continuous antibiotic regimen has been shown⁵. The effect of continuous *versus* intermittent dosing on the inflammatory response during sepsis has not been examined previously.

Organ failure subsequent to sepsis has been attributed to the systemic inflammatory response syndrome due to Gram-negative aerobes, endotoxin and the circulatory release of proinflammatory cytokines such as tumour necrosis factor (TNF) α and interleukin (IL) 1β ^{6–8}. This is based on animal models using challenge with Gram-negative bacteria or endotoxin^{9,10}. In contrast, after experimental faecal peritonitis (caecal ligation and puncture (CLP)), there are very low serum levels of TNF- α or IL- 1β , but a local sustained increase in organ (lung and liver) expression of TNF- α and IL- 1β messenger RNA (mRNA)^{11–13}. Local production of these cytokines may upregulate neutrophil and endothelial adhesion molecules causing neutrophil sequestration¹⁴. After CLP, neutrophils sequester in the lung and injury has been shown to be, in part, neutrophil dependent¹⁵. Bacteraemia secondary to faecal peritonitis is typically polymicrobial¹⁶. Although the anaerobic component has been shown experimentally to potentiate the toxicity of the Gram-negative component¹⁷, evidence of a direct effect of anaerobes on the systemic inflammatory response is lacking.

It was hypothesized that a continuous infusion of antibiotic after CLP would reduce lung IL- 1β and TNF- α expression and neutrophil sequestration compared with intermittent dosing, and that increased expression of lung IL- 1β and TNF- α mRNA and associated neutrophil sequestration after CLP would be caused or potentiated by anaerobic bacteria.

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Materials and methods

Care of animals

Adult male Swiss Webster mice (Taconic, Germantown, New York, USA), weighing 25–30 g, were used for all experiments. Animals were housed in an American Association for Accreditation of Laboratory Animal Care-approved facility and provided food and water *ad libitum*. Studies were carried out according to the National Institutes of Health guidelines and under the supervision of a veterinarian.

Caecal ligation and puncture model

CLP was performed as described previously¹¹. Briefly, the caecum was exposed through a midline laparotomy, ligated at its base and punctured twice with an 18-G needle before replacement intraperitoneally.

Trial design

Mice were randomized to receive continuous cefoxitin ($n=7$), intermittent cefoxitin ($n=7$) or saline (saline control, $n=7$) at the time of CLP, or no treatment (normal control, $n=7$) (experiment 1). Experiment 1 was repeated, with similar results being obtained. Then, mice were randomized to receive continuous metronidazole ($n=14$), aztreonam ($n=14$) or saline (saline control, $n=14$) commenced before CLP, or no treatment (normal control, $n=7$) (experiment 2). The authors have previously shown that sham operation alone does not alter lung neutrophil sequestration, serum TNF- α , organ TNF- α or IL-1 β mRNA expression when compared with values in normal mice¹². Administration of antibiotics in experiment 2 was not used as treatment but as a tool to investigate a mechanism of action, and therefore pretreatment was considered more appropriate. Use of aztreonam was chosen for experiment 2 because of a decision to target Gram-negative aerobes rather than Gram-negative aerobes and anaerobes and Gram-positive aerobes, as with cefoxitin in experiment 1.

Experiment 1: intermittent or continuous infusion of cefoxitin Following CLP, cefoxitin 200 mg per kg per day was administered subcutaneously, either three times daily or via a micro-osmotic pump placed at the time of CLP (Alzet model 1003D, Alza Corporation, Palo Alto, California, USA). Subcutaneous administration of a similar cephalosporin has been shown to achieve similar plasma levels of antibiotic as found after intravenous injection¹⁸. Control animals received equal volumes of saline or had no procedure performed. Mice were killed 24 h after CLP.

Experiment 2 continuous infusion of metronidazole or aztreonam Two hours before CLP mice received an intraperitoneal injection of 0.8 mg aztreonam, 0.6 mg metronidazole or 0.2 ml of saline. Following CLP, aztreonam 200 mg per kg per day or metronidazole 130 mg per kg per day was administered continuously via a micro-osmotic pump placed intraperitoneally at the time of surgery. Control animals received equal volumes of saline via a micro-osmotic pump or had no procedure performed. Mice were killed 6 and 24 h after CLP.

Total tissue RNA extraction

Tissue extraction was performed according to the method described by Chomczynski and Sacchi¹⁹, using whole right lung.

Semiquantitation of interleukin 1 β and tumour necrosis factor α messenger RNA

This is a semiquantitative competitive differential polymerase chain reaction (PCR)-based protocol adapted to quantitate murine TNF- α and IL-1 β mRNAs^{11,20}. Briefly, total cellular RNA (400 ng) was transcribed reversely (Perkin-Elmer, Norwalk, Connecticut, USA), and for PCR of the complementary DNA

(cDNA), primers (TNF- α , IL-1 β , β -actin or GAPDH (glyceraldehyde phosphate dehydrogenase)) were added in the same tube and amplified for 29 cycles. To ensure that the amount of cytokine cDNA was measured only during the exponential phase of the PCR amplification, the optimum number of PCR cycles was determined for each primer pair before amplification^{11,12}. To ensure there was no amplification of contaminating genomic DNA, control samples were run for each primer pair without the addition of reverse transcriptase. The ratios for cytokine: β -actin or GAPDH were calculated from densitometric analysis of negative films following electrophoresis and ethidium bromide staining of the PCR products.

Serum tumour necrosis factor α assay

TNF- α levels were determined by the WEHI 164 subclone 13 cell line bioassay as described by Eskandari *et al.*²¹

Serum endotoxin assay

Endotoxin levels were determined in 1:10 dilutions of mouse serum by the chromogenic limulus amoebocyte assay (QCL-1000; BioWhittaker, Walkersville, Maryland, USA), according to the manufacturer's protocol.

Myeloperoxidase assay

To quantify accurately the number of neutrophils within the lung, the myeloperoxidase (MPO) assay was performed on tissue from the right lower lung as described previously²².

Blood cultures

Blood samples, obtained by cardiocentesis, were plated on tryptic soy agar for aerobic culture or on brain heart infusion agar for anaerobic culture. Colony forming units (CFUs) were determined by manual counting of the plates and results were expressed in CFUs per millilitre of blood.

Statistical analysis

mRNA and blood culture differences were analysed with the Mann-Whitney *U* test. MPO, endotoxin and TNF- α levels were compared with Student's *t* test. Data are presented as median (range). Differences were considered significant when $P < 0.05$.

Results

Experiment 1: intermittent or continuous infusion of cefoxitin

Lung tumour necrosis factor α and interleukin 1 β messenger RNA expression. Continuous cefoxitin treatment significantly reduced IL-1 β mRNA but not TNF- α expression compared with intermittent dosing (Table 1).

Serum tumour necrosis factor α concentration. All groups showed raised serum TNF- α levels at 24 h compared with normal mice and there were no differences between groups (Table 2).

Lung myeloperoxidase levels. In animals receiving continuous cefoxitin, lung MPO concentration was significantly reduced compared with that in the intermittently treated group at 24 h (Table 1).

Serum endotoxin and blood cultures. Intermittent cefoxitin significantly reduced serum endotoxin concentration at 24 h compared with that in saline controls (Table 2). In contrast, continuous infusion of cefoxitin

Table 1 Lung tumour necrosis factor α and interleukin β messenger RNA expression, and myeloperoxidase levels, 24 h after caecal ligation and puncture: effect of continuous *versus* intermittent cefoxitin administration

Group (<i>n</i> = 7 per group)	TNF- α mRNA	IL-1 β mRNA	MPO (units/g)
Normal control	0.02 (0.007–0.03)	0.015 (0.01–0.016)	13 (6–19)
Saline control	0.46 (0.38–0.57)	0.43 (0.38–0.53)	47 (41–64)
Intermittent cefoxitin (200 mg per kg per day)	0.44 (0.40–0.56)	0.46 (0.44–0.49)	65 (57.5–76)
Continuous cefoxitin (200 mg per kg per day)	0.39 (0.37–0.49)	0.18 (0.14–0.34)*	22.5 (9.7–40)†

Values are median (interquartile range); interleukin (IL) 1 β and tumour necrosis factor (TNF) α are expressed as a ratio to β -actin. mRNA, messenger RNA; MPO, myeloperoxidase. **P* < 0.05 *versus* intermittent cefoxitin and saline control (Mann–Whitney *U* test); †*P* < 0.05 *versus* intermittent cefoxitin and saline control (Student's *t* test)

Table 2 Blood cultures, serum endotoxin and serum tumour necrosis factor α levels: effect of continuous *versus* intermittent cefoxitin administration 24 h after caecal ligation and puncture

Group (<i>n</i> = 7 per group)	Blood culture (log CFUs/ml)*	Serum endotoxin (units/ml)	Serum TNF- α (pg/ml)
Normal control	—	0.2 (0.1–0.2)	ND
Saline control	4.9 (4.8–4.9)	2.9 (1.5–4.3)	52.6 (37.8–129.4)
Intermittent cefoxitin (200 mg per kg per day)	3.7 (3.3–4.8)	0.1 (0.1–0.3)‡	33.3 (26.3–79.1)
Continuous cefoxitin (200 mg per kg per day)	2.6 (2.0–3.7)†	3.0 (0.1–2.7)	68.7 (43.9–98.2)

Values are median (interquartile range). *Cultures reflect colony forming units (CFUs) of aerobic and anaerobic plates. TNF- α , tumour necrosis factor α ; ND, none detected. †*P* < 0.05 *versus* saline control (Mann–Whitney *U* test); ‡*P* < 0.05 *versus* saline control and continuous cefoxitin (Student's *t* test)

Table 3 Effect of continuous metronidazole or aztreonam administration on blood cultures and serum endotoxin concentration 24 h after caecal ligation and puncture and on serum tumour necrosis factor α levels 6 h after caecal ligation and puncture

Group	Blood culture (log CFUs/ml)		Serum endotoxin (units/ml)	Serum TNF- α (pg/ml)
	Aerobic	Anaerobic		
Normal (<i>n</i> = 7)	—	—	0.1 (0.1–0.2)	ND
Saline control (<i>n</i> = 14)	6.2 (5.2–7.0)	6.2 (5.4–7.0)	18.0 (13.2–25.5)	8.05 (5.3–17.3)
Continuous metronidazole (<i>n</i> = 14)	2.7 (0.7–3.6)*	2.6 (1.4–3.9)*	15.5 (5.4–17.3)	11.3 (6.8–18.2)
Continuous aztreonam (<i>n</i> = 14)	2.9 (2.6–4.4)*	4.1 (3.3–4.9)*	7.1 (5.8–11.3)†	3.7 (3.9–6.1)

Values are median (interquartile range). CFUs, colony forming units; TNF- α , tumour necrosis factor α ; ND, none detected. **P* < 0.05 *versus* saline control (Mann–Whitney *U* test); †*P* < 0.05 *versus* saline control (Student's *t* test)

significantly reduced blood cultures as measured quantitatively, compared with intermittent dosing (Table 2).

Experiment 2: continuous infusion of metronidazole or aztreonam

Lung tumour necrosis factor α and interleukin 1 β messenger RNA expression. Metronidazole-treated mice expressed significantly less lung TNF- α (Fig. 1) and IL-1 β mRNA (Fig. 2) at 24 h than saline controls. Aztreonam-treated mice expressed significantly less IL-1 β mRNA at 6 h and less TNF- α mRNA at 24 h than saline controls (Figs 1 and 2).

Lung myeloperoxidase levels. At 24 h both antibiotic-treated groups showed significantly less lung MPO activity than saline controls (Fig. 3).

Serum tumour necrosis factor α levels. Serum TNF- α concentration, 6 h after CLP, was raised in all groups and,

although it was reduced in the aztreonam-treated mice, this was not statistically significant (Table 3).

Serum endotoxin concentration. Serum endotoxin was increased 24 h after CLP in all treatment groups. Aztreonam-treated animals had significantly lower levels than saline controls (Table 3).

Blood cultures. Bacteraemia was predominantly anaerobic early after CLP (6 h) (data not shown). By 24 h significant numbers of aerobic bacteria had been cultured. Aztreonam and metronidazole inhibited both anaerobes and aerobes at 24 h (Table 3).

Discussion

These data indicate that bacteraemia (anaerobic or aerobic) rather than serum endotoxin concentration determines an organ's proinflammatory cytokine response and hence neutrophil sequestration. The lack of correlation

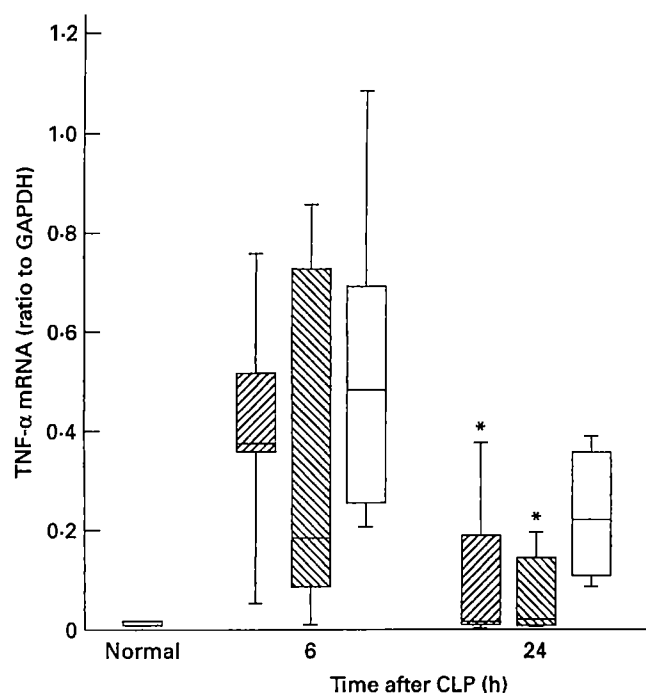


Fig. 1 Effect of continuous metronidazole (▨) or aztreonam (▧) administration on lung tumour necrosis factor (TNF) α messenger RNA (mRNA) expression after caecal ligation and puncture (CLP). TNF- α mRNA is expressed as the ratio to GAPDH (glyceraldehyde phosphate dehydrogenase). Median (range – 10th to 90th percentiles) values are shown. □, Saline control. * $P < 0.05$ versus saline control (Mann–Whitney U test)

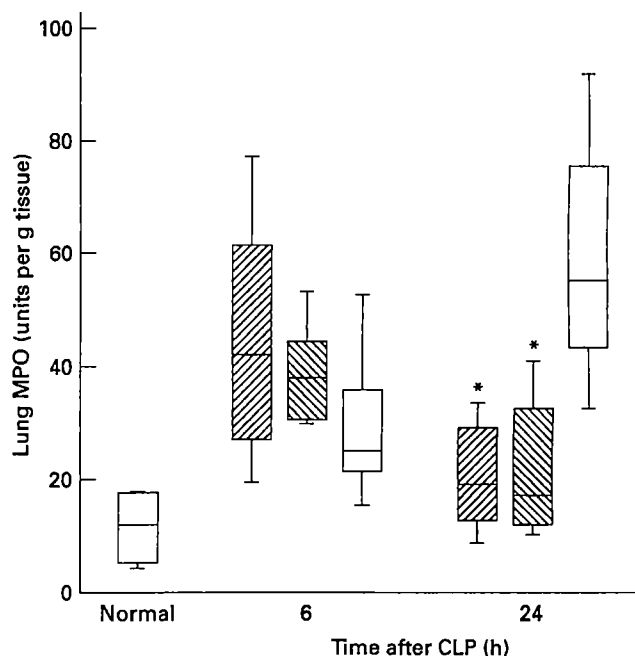


Fig. 3 Effect of continuous metronidazole (▨) or aztreonam (▧) therapy on lung myeloperoxidase (MPO) content after caecal ligation and puncture (CLP). Values are median (range – 10th to 90th percentiles) values are shown. □, Saline control. * $P < 0.05$ versus saline control (Student's t test)

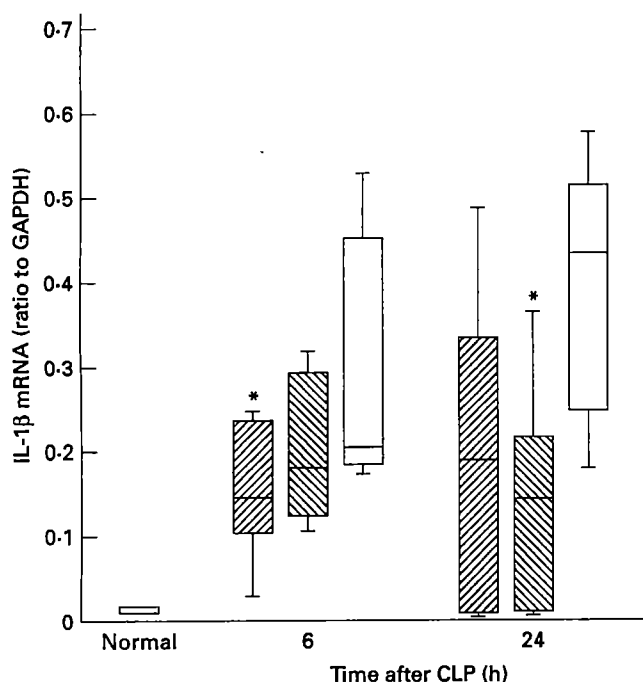


Fig. 2 Effect of continuous metronidazole (▨) or aztreonam (▧) administration on lung interleukin (IL) 1 β messenger RNA (mRNA) expression after caecal ligation and puncture (CLP). IL-1 β mRNA is expressed as the ratio to GAPDH (glyceraldehyde phosphate dehydrogenase). Median (range – 10th to 90th percentiles) values are shown. □, Saline control. * $P < 0.05$ versus saline control (Mann–Whitney U test)

between serum TNF- α levels and (1) bacteraemia, (2) organ IL-1 β or TNF- α mRNA expression or (3) neutrophil sequestration lends further support to the importance of organ overexpression of these cytokines rather than systemic release in a clinically relevant sepsis model.

Both experiments question the importance of raised serum levels of endotoxin and cytokines during sepsis. Correlations between organ proinflammatory cytokine mRNA expression and neutrophil sequestration were observed and these were independent of serum endotoxin or TNF- α levels. The relationship between serum endotoxin levels and outcome in human sepsis studies has recently been questioned²³ and, although circulating cytokine concentrations (TNF- α , IL-1 β , IL-6) have been reported to be of predictive value in human sepsis studies, only measurement of serum IL-6 concentration has been of consistent value²⁴. An even more important hypothesis is whether the serum cytokine response sometimes observed during sepsis represents merely an 'overflow' of cytokines from the tissues or whether tissue levels provide more accurate information on the state of the host response. In fact, the serum levels may represent only the 'tip of the iceberg'²⁵.

The effectiveness of continuous *versus* intermittent antibiotic administration is supported by the consistent results of other investigators^{3,4}. The efficacy of cephalosporins is predominantly concentration independent but is dependent on the length of time for which tissue or serum antibiotic concentration is above the minimum inhibitory concentration (MIC)²⁶. The area under the concentration curve is similar with intermittent *versus* continuous infusion; however, the shape of the curve is different, with continuous infusion achieving a more sustained level above the MIC. In general, the short half-life of

cephalosporins and β -lactams favours rapid clearance, and thus intermittent dosing allows for regrowth of Gram-negative bacilli whenever the concentrations are below MIC or minimum bactericidal concentration²⁷. These factors, in addition to the lack of a postantibiotic effect, are further arguments for continuous administration of cephalosporins^{27,28}.

Experimental evidence to link a direct effect by anaerobes on the systemic inflammatory response is lacking. Weinstein *et al.*²⁹ showed that, in a polymicrobial peritonitis model, clindamycin reduced abscess formation, whereas gentamicin reduced mortality. Rotstein and Kao¹⁷ discussed the anaerobic component of peritonitis as being important only in the context of potentiating the pathogenicity of the Gram-negative aerobic component. The present data show a direct effect by anaerobes on organ inflammatory cytokine induction and neutrophil sequestration as metronidazole therapy had a greater effect on lung cytokine mRNA expression without reducing serum endotoxin levels compared with aztreonam.

In summary, continuous administration of cefoxitin during septic peritonitis reduced bacteraemia, lung IL-1 β mRNA expression and lung neutrophil sequestration compared with intermittent dosing. In the same model, treatment with continuous infusion of metronidazole or aztreonam reduced lung IL-1 β and TNF- α mRNA expression as well as neutrophil sequestration. As the search continues for new and effective therapies for the prevention of organ failure after peritonitis, modification of existing antibiotic dosing treatments seems useful and a very overlooked, clinically viable, option.

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Infiltrating lobular carcinoma of the breast detected by screening

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Background This study was a retrospective analysis of all patients with invasive lobular breast cancer who presented to the University Hospital Nijmegen between 1980 and 1990, with follow-up to December 1992. A comparison was made between the invasive lobular carcinomas detected by breast cancer screening and those detected outside the screening project.

Methods The total number of patients with breast cancer during this interval was 937, of whom 136 (14.5 per cent) had pure infiltrating lobular carcinoma (ILC). Breast cancer screening identified a total of 158 patients with infiltrating breast carcinoma of whom 20 (12.7 per cent) had ILC. Outside the screening programme a total of 116 patients with ILC were diagnosed during the same interval.

Results The 2- and 5- and 10-year disease-free survival rate in the screen-detected group was 100, 100 and 89 per cent respectively. For the group outside the screening programme this was 88.4, 74.3 and 72.5 per cent respectively ($P = 0.04$). No patient in the screen-detected group died from breast cancer during follow-up, whereas the 2- and 5- and 10-year breast cancer survival rate for the group detected outside the screening programme was 96.5, 89.1 and 70.6 per cent respectively ($P = 0.06$).

Conclusion Between 10 and 15 per cent of patients with invasive lobular breast cancer can be detected by breast screening. These patients have a favourable outcome compared with those who have ILC detected outside the screening programme.

Infiltrating lobular carcinoma (ILC) of the breast comprises 5–10 per cent of all breast carcinomas^{1,2}. It is difficult to detect ILC both clinically and at mammography. Mammographic screening is thought to be less effective for detecting ILC in an early stage compared with invasive ductal carcinoma (IDC). This study examined the role of mammographic screening in detecting ILC at an early stage. The records of all patients who presented with pure ILC during 11 years were reviewed retrospectively.

Patients and methods

Between January 1980 and December 1990 a total of 937 patients were referred with primary breast cancer. Data were evaluated through to the end of December 1992, with follow-up ranging from 1 to 12 (mean 5.6) years. Patient age at detection varied from 35 to 89 (mean 58) years. In Nijmegen a population screening programme invites women aged between 50 and 70 years to attend for bi-annual mammography, which consists of single view films of each breast in the mediolateral oblique projection. From the total of 937 cases of infiltrating breast carcinoma, 158 were detected by mammographic screening; 20 (12.7 per cent) were ILCs. In total 136 patients (14.5 per cent) were diagnosed with pure ILC. Patients with mixed infiltrating ductal carcinoma and ILC were not included in this study. The 136 patients with ILC were divided into two groups: the 20 detected by screening mammography and the remaining 116 identified outside the screening programme, who either presented with a palpable mass or whose lesion was an incidental finding following biopsy for a benign lesion. Outcome was determined in each of these two groups.

Other clinical features examined included tumour size as assessed on the pathology report, axillary node status (positive apical, level III nodes were registered separately) and oestrogen receptor status. The latter was negative if less than 10 fmol/mg. Progesterone receptor status was negative if less than 30 fmol/mg.

The surgical treatment for ILC has changed during the study. A modified radical mastectomy was done initially in both groups. For smaller tumours treatment has evolved towards breast conservation. Adjuvant irradiation of the axilla was given when there was extranodal tumour. Adjuvant chemotherapy was administered to premenopausal women with axillary lymph node involvement, and in postmenopausal women tamoxifen was used.

Results

Of the 136 patients with ILC, 20 (14.7 per cent) were detected by the screening programme, and 116 (85.3 per cent) were diagnosed outside the screening programme. Fourteen patients presented with an interval carcinoma and were classified as diagnosed outside screening.

Only 43 patients (31.6 per cent) had stage pT₁ (2 cm or less) tumours. In the screen-detected group, 60 per cent had a stage T₁ tumour compared with 29.8 per cent in the remainder (Table 1). Twelve tumours in the non-screen-detected group could not be sized. Axillary lymph node

Table 1 Tumour characteristics for patients with infiltrating lobular carcinoma

	Screen detected	Detected outside screening
Tumour stage*		
T ₁ (≤ 2 cm)	12 (60)	31 (29.8)
T ₂ (2–5 cm)	5 (25)	43 (41.3)
T ₃ (> 5 cm)	3 (15)	30 (28.8)
Node status		
Positive axillary lymph nodes	6 (30)	63 (57.8)
Involved level III nodes	3 (15)	27 (24.8)
Positive oestrogen receptor status	18 (100)	82 (79.6)
Positive progesterone receptor status	9 (50)	50 (44.0)

Values in parentheses are percentages. *Exact tumour size could not be assessed in 12 patients

status is compared between the groups in Table 1. Information on nodal status was not available for seven patients. Two patients had lymph node metastases at presentation, one had a stage pT₁ tumour and one a stage pT₃ lesion. In the group aged between 50 and 70 years (screening age), 26 of the 46 patients with ILC detected outside screening had lymph node involvement, compared with 23 of the 39 patients aged under 50 years. Oestrogen receptor status was measured in 121 patients and progesterone receptor status in 120 of the 136 patients (Table 1).

The 2-, 5- and 10-year disease-free survival rate for the screen-detected group was 100, 100 and 89 per cent respectively ($P=0.04$) (Fig. 1). Only one patient in the screen-detected group developed recurrent breast cancer. For patients with ILC detected outside screening, the 2-, 5- and 10-year disease-free survival rate was 88.4, 74.3 and 72.5 per cent respectively. The hazard ratio for disease-free survival was 6.19 in the screen-detected group ($P=0.01$; 95 per cent confidence interval less than 1 to more than 6.2). Survival rates were also calculated: no patient in the screen-detected group died. For patients with ILC detected outside screening the 2- and 5-year breast cancer survival rate was 96.5 and 89.1 per cent respectively ($P=0.06$) (Fig. 2).

There were no significant differences in survival in patients with ILC detected outside the screening programme when patients aged under 50 years were compared with those aged over 50 years (5-year disease-free survival rate 72 versus 75 per cent; 10-year disease-free survival rate 63 versus 62 per cent respectively).

Discussion

Because invasive lobular carcinoma represents only a minority of invasive breast carcinomas (5–10 per cent) few studies deal with clinical aspects of this tumour. ILC is a fairly homogeneous small-cell tumour of low nuclear grade with a more favourable prognosis than IDC³. There is a higher incidence of bilaterality and one-third of the

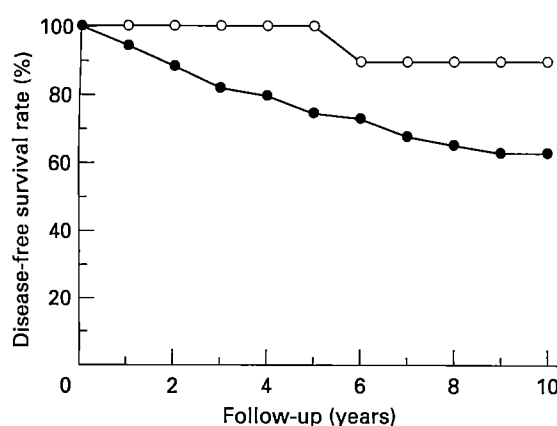


Fig. 1 Comparison of disease-free survival in patients with infiltrating lobular carcinoma (ILC) detected by screening ($n=20$; ○) and in those with ILC detected outside the screening programme ($n=116$; ●). $P=0.04$, Kaplan-Meier

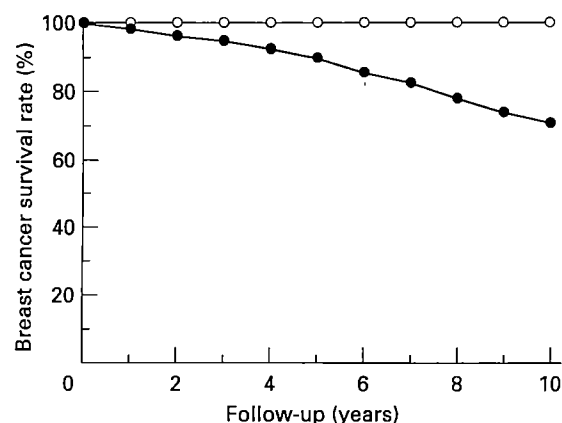


Fig. 2 Comparison of breast cancer survival in patients with infiltrating lobular carcinoma (ILC) detected by screening ($n=20$; ○) and in those with ILC detected outside the screening programme ($n=116$; ●). $P=0.06$

patients have multifocal and multicentric tumours. Breast conservation has the same results as ablative surgery and is an appropriate choice for ILC in selected patients^{4,5}.

That 12.7 per cent of the carcinomas were detected by screening proves that ILC can be identified by mammography. This figure is similar to other reported values^{6,7}. ILC is an insidious tumour, more difficult to palpate and visualize than IDC, both clinically and at mammography. This is because there is a less pronounced desmoplastic reaction which makes the tumour rubbery and less well defined. The tumour is less easily visualized on mammography because it has a low radiographic opacity^{2,3,8}. Some 1.3 per cent of IDCs are mammographically occult compared with 8 per cent of ILCs. ILC was larger than 2 cm in 70 per cent in a previous report⁸. Microcalcifications are seldomly associated with ILC compared with ductal cancer⁹. The rate of mammographic detection of ILC in this study may be attributed to the relatively high mean age of the patients (58 years) which makes the breast more accessible for mammography because of glandular involution. ILC in the dense breasts of young women may be more difficult to detect⁸. In this screening centre single oblique view mammograms were routine, based on the fact that the axillary tail is easily visible. Two view mammography might have detected more tumours. Single view mammography has been routine in Nijmegen since 1975^{10,11}. Magnetic resonance mammography may be advantageous; in a small study it was shown to detect ILC in mammographically negative breasts and to give a more exact determination of the tumour size¹².

Some 60 per cent of the ILCs were detected by screening at the T₁ stage while 70.2 per cent detected outside screening were T₂ or T₃ lesions. The mean size of the screen-detected ILCs was 2 cm compared with 3 cm for the non-screen-detected carcinomas. In an earlier study, in which 90 per cent were IDCs, 66 per cent of the lesions in the screened group were stage T₁, while 57 per cent of the cancers that were detected outside the screening programme were stage T₂ or T₃¹³.

Only 30 per cent of the patients with ILC detected with screening mammography had axillary lymph node metastases in contrast to almost 58 per cent of the non-screened group. This resulted in an almost 100 per cent disease-free survival rate in the screened population. There was no difference in survival between those with T₁ lesions in the screened group (12 patients) and the non-screened group (31 patients), probably because of the small sample size. In addition there was a lead time bias effect in the screen-detected group. It is still debatable whether screen-detected carcinomas have a more favourable prognosis. Studies which claim a biological difference between screen-detected and other carcinomas are based on the findings that screen-detected carcinomas have better differentiation, less tumour necrosis, a lower mitotic count and a higher concentration of oestrogen and progesterone receptors. Screen-detected tumours are more often diploid and have a smaller S-phase fraction¹⁴. Expression of cathepsin D, a protein regulated by oestrogens, is also increased in screen-detected tumours¹⁵. In this study all screen-detected ILCs were oestrogen receptor positive compared with 79.6 per cent of tumours found outside screening. Progesterone receptor activity was similar between the groups. Receptor activity is more frequently raised in small tumours, which suggests that every breast tumour initially contains receptors, levels of which decrease in advanced stages¹⁶.

In patients aged between 50 and 70 years invasive lobular carcinoma can be detected by screening mammography with a rate similar to that for invasive ductal cancers. Screening detects ILC at an earlier disease stage with the possibility of improved prognosis.

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Anatomical variants during axillary dissection

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Background This study was done to document the variations encountered in the anatomy of the axilla because of the difficulty they can cause during dissection.

Methods A record was made of the anatomy of the axilla in 100 patients with breast cancer who had an axillary dissection.

Results The variants from the described normal included double axillary veins, abnormal bands of muscle from the latissimus dorsi stretching across the axilla and a medial lying thoracodorsal nerve.

Conclusion Damage to important structures in the axilla during axillary dissection can be minimized with an awareness of the possible anatomical variations.

Variations in axillary anatomy have not been described in most texts of operative surgery¹ or anatomy^{2,3}. However, there is great potential for damage to important structures in this region for the unwary or inexperienced surgeon. The anatomy of this area was studied in 100 patients and the findings documented.

Patients and methods

The anatomy of the axilla was documented in 100 patients who had an axillary dissection as part of staging and treatment of invasive primary breast cancer over 6 months.

The axillary dissection was performed in continuity with a mastectomy or through a separate axillary incision if the breast was conserved. A level 1 axillary dissection was done unless it was known that the nodes were involved when a full clearance was performed. The axillary vein was identified and all fatty/lymphatic tissue harvested inferior to the vein, between the anterior border of the latissimus dorsi muscle laterally and the lateral border of the pectoralis minor (level 1) or first rib (clearance) medially. The thoracodorsal neurovascular bundle and long thoracic nerve were identified and preserved. The intercostobrachial nerve was identified and preserved, if possible. Any anatomical variant found during operation was recorded.

Results

Of the 100 patients, 29 had a variation from the standard anatomy as described in the textbooks of anatomy and operative surgery.

Abnormal axillary vein(s)

There were 21 patients in this group. Ten had double axillary veins lying below the axillary artery (Fig. 1). In nine the two veins united at the lateral border of pectoralis minor to form a single large vein. In two patients no large vein was seen in the axilla but a leash of three or more vessels was observed. In patients with an abnormal axillary vein, the thoracodorsal vein originated from the lower vein in 14 and the upper vein in three patients. The origin was not clear in the remaining four patients.

Abnormal muscle or tendon

There were six patients who had an abnormal band of muscle and/or tendon stretching across the axilla. In two this arose from the latissimus dorsi muscle and crossed the axilla medially towards the pectoralis minor to insert into the coracoid process (Fig. 1). In the others it lay across the axilla passing from the latissimus dorsi, over the axillary vein, to the pectoralis major muscle. In one of these patients there was also a double axillary vein.

Abnormal location of the thoracodorsal nerve

In five patients the nerve supplying the latissimus dorsi muscle ran between 2 and 3 cm medial to the thoracodorsal vessels, not joining the vessels until close to the point of insertion into the muscle (Fig. 1). In two of these patients this was associated with a double axillary vein.

Discussion

The technique for axillary dissection involves removing all lymphatic tissue inferior to the axillary vein¹. In patients with a double axillary vein it is possible to identify the upper vein initially and, during the subsequent dissection,

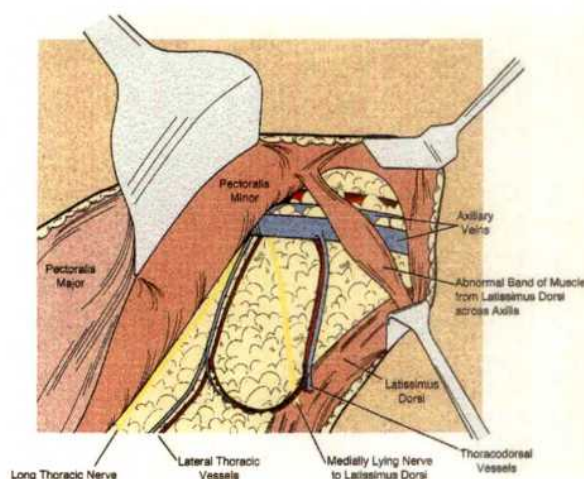


Fig. 1 Anatomical variations in the axilla

the lower vein is at risk of damage with consequent haemorrhage and risk of damage to the latissimus dorsi neurovascular bundle. Gentle dissection of tissues with a reluctance to divide any horizontally lying veins should allow this anomaly to be identified and prevent inadvertent damage.

An abnormal band of muscle or tendon has been described previously arising, from the edge of the latissimus dorsi, midway in the posterior axillary fold, crossing over the front of the axillary vessels and nerves to join the tendon of the pectoralis major, coracobrachialis or fascia over the biceps⁴. This band can easily cause difficulty for the inexperienced surgeon particularly if, by following the band, the dissection is carried higher than normal, into the region of the axillary artery and brachial plexus.

It is important that the thoracodorsal nerve and vessels are preserved during axillary dissection to preserve function and to allow later reconstructive surgery using a latissimus dorsi flap. Division of the nerve, even if the vessels are preserved, would lead to muscle atrophy. The

thoracodorsal nerve usually joins the artery and vein from the medial side just below the axillary vein. In 5 per cent of patients there was a distance of between 2 and 3 cm between nerve and vessels. It is therefore necessary to proceed with caution until the thoracodorsal nerve and its relationship to the vessels has been identified.

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Abdominal lymphangioma in adults and children

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Background Abdominal lymphangioma is a rare tumour usually classified with mesenteric and retroperitoneal cysts. This experience of abdominal lymphangiomas contrasts the differences between tumours in children and adults.

Methods Between 1970 and 1996, six patients had surgical resection of an abdominal lymphangioma.

Results There were three children aged 4 years or less and three adults aged 36–76 years. Two children presented with an acute abdomen and one with a rapidly enlarging abdominal girth. Lymphangiomas were located in the mesentery and gastrointestinal tract. In adults, symptoms lasted from months to years and lymphangiomas were found in the pancreas, spleen and retroperitoneum.

Conclusion In this series, abdominal lymphangioma presented more acutely in children and usually involved the mesentery, whereas in adults the history was longer and the tumour was found in the retroperitoneum.

Abdominal lymphangioma is rare and often classified with mesenteric and retroperitoneal cysts. The tumour can occur at any age and most are asymptomatic¹. Recent reports indicate that abdominal lymphangioma differs significantly from other mesenteric cysts^{2,3}. They are more common in children and are symptomatic in up to 88 per cent of cases^{4–6}. Benign cystic mesothelioma and simple mesothelial cysts tend to occur in middle-aged women and remain asymptomatic^{2,7}. This report of six patients with abdominal lymphangioma contrasts characteristics and differences between tumours in adults and children.

Patients and methods

Between 1970 and 1996, six patients (three children, three adults) had surgical resection of an abdominal lymphangioma. The diagnosis of cystic lymphangioma was made using five standard histological criteria: (1) cyst lined by a flat endothelial epithelium; (2) small lymphatic spaces; (3) abundant lymphoid tissue; (4) smooth muscle present in the cyst wall; and (5) foam cells containing lipid material present in varying number. The clinical details of the six patients are recorded in Table 1.

Results

Two of the children presented as an emergency with acute abdominal pain; the third had pain and rapidly increasing abdominal girth. The only preoperative investigation was a plain abdominal radiography. At operation the lymphangiomas were located in the ileal mesentery ($n=2$) and stomach ($n=1$) (Fig. 1). All were resected entirely with either part of the mesentery or the stomach.

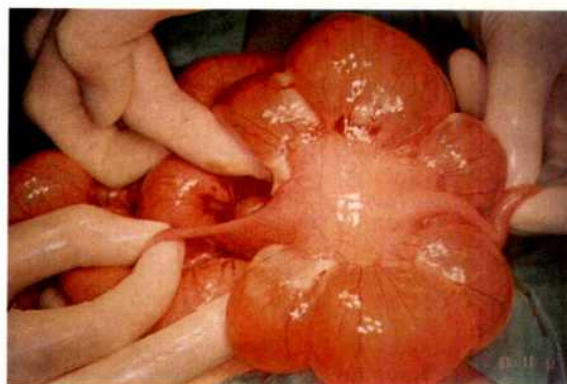


Fig. 1 Lymphangioma of the mesentery in a 3-year-old girl

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Table 1 Characteristics of the six patients

Patient no.	Age (years)	Sex	Location	Symptoms	Clinical signs	Duration of symptoms	Surgery	Outcome	Length of follow-up (years)
1	3	F	Mesentery	Abdominal pain	Peritonitis, abdominal mass	Acute	Total excision, ileal resection	Alive and well	4
2	3	F	Stomach	Abdominal pain	Peritonitis	Acute	Total excision, gastric resection	Alive and well	16
3	4	F	Mesentery	Abdominal pain	Increased abdominal girth	10 days	Total excision, ileal resection	Alive and well	5
4	36	F	Pancreas	Abdominal pain	Abdominal mass	1 month	Total excision, left splenopancreatectomy	Alive and well	1
5	56	F	Spleen	Vomiting	None	5 years	Total excision, splenectomy	Alive and well	11
6	76	M	Retroperitoneum	Dyspnoea	Abdominal mass	3 years	Partial excision	No recurrence	7

Table 2 Histopathological findings

Patient no.	Location of lymphangioma	Size of lymphangioma (cm)	Type of lymphangioma	Flat epithelial endothelium	Lymphoid tissue	Lymphatic spaces	Smooth muscle	Foam cells
1	Mesentery	11 × 10 × 6	Cystic	Present	Present	Present	Absent	Absent
2	Stomach	20 × 10 × 8	Cystic	Present	Present	Absent	Absent	Absent
3	Mesentery	13 × 13 × 8	Cystic	Present	Absent	Present	Absent	Absent
4	Pancreas	18 × 14 × 7	Cystic	Present	Present	Absent	Present	Absent
5	Spleen	4 × 4 × 3	Cystic	Present	Present	Absent	Absent	Present
6	Retroperitoneum	17 × 16 × 8	Cystic	Present	Present	Absent	Present	Absent

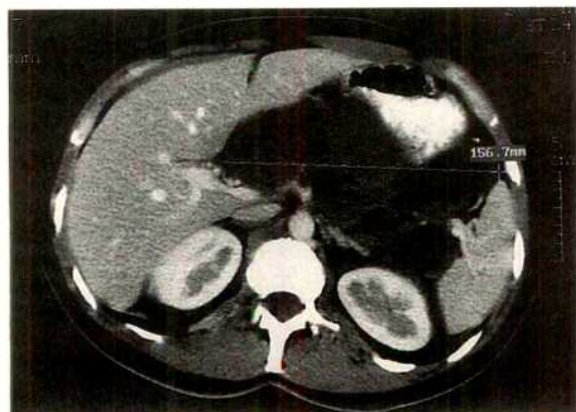


Fig. 2 Computed tomogram of lymphangioma of the pancreas

All three adults had had long-standing symptoms for months or years. Ultrasonography and computed tomography were the most helpful investigations (Fig. 2). Lymphangiomas in the pancreas ($n = 1$) and spleen ($n = 1$) were resected entirely by left splenopancreatectomy and splenectomy respectively. The lymphangioma of the retroperitoneum was resected only partially because of adherence to the vena cava and common iliac artery. In the latter patient there is no evidence of recurrence after 7 years. Details of the histological findings are shown in Table 2.

Discussion

The most common sites for lymphangioma are the neck and axilla, which account for 95 per cent of cases⁴. The remaining 5 per cent occur sporadically in the lungs, mediastinum, adrenal glands, kidneys or bone. Abdominal lymphangiomas are rare but have been reported in the mesentery⁶, gastrointestinal tract⁸, retroperitoneum⁹, spleen¹⁰, liver¹¹ and pancreas¹². Gastric lymphangioma in a child is extremely rare¹³.

Lymphangiomas result from a developmental failure of the lymphatic system and have recently been differentiated from mesenteric cysts, which originate from mesothelial tissue^{2,3,7}. Lymphangiomas are characterized histologically by a flat epithelial endothelium and a wall containing alternatively lymphoid tissue, small lymphatic spaces, smooth muscle and foam cells². In these patients, lymphoid tissue was present in most lymphangiomas, whereas lymphatic spaces were common in children and smooth muscle in adults (Table 2).

The present series, although small, confirms recent reports that the presentation of abdominal lymphangioma

is usually of short duration in children⁴⁻⁶. Adults, on the other hand, seldom had abdominal pain and their clinical complaints evolved over months to years before diagnosis. Lymphangiomas were located in the mesentery or gastrointestinal tract in children, whereas in adults they were located in the retroperitoneum or retroperitoneal organs. These differences are not exclusive, as children with mesenteric lymphangioma may present with progressive abdominal distension⁴, and retroperitoneal lymphangioma has been described in neonates¹⁴.

Preoperative diagnosis was facilitated by ultrasonography and computed tomography: thickness of the cyst wall, number of cystic septations and internal echos may differentiate lymphangioma from other mesenteric cysts^{7,15}. In future, magnetic resonance imaging could enable better preoperative evaluation of cystic tumours⁷.

Aspiration, drainage and irradiation of lymphangioma gives poor results; therefore complete excision is the treatment of choice¹⁶. Surgery should be undertaken promptly unless the cyst has recently been infected, in which case a 3-month wait has been recommended¹⁶. Although benign, abdominal lymphangioma may become locally invasive. Resection of the involved organ is therefore required. If major resection of a vital organ is necessary, internal peritoneal cavity marsupialization may occasionally be an acceptable alternative¹⁷.

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Reconstruction after total gastrectomy by the interposition of a double jejunal pouch using a double stapling technique

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Background After total gastrectomy, sustaining good nutrition is extremely important for maintaining quality of life. A technique of neogastric pouch formation based on current physiological reconstructive principles is presented.

Methods The use of a modified interpositioned double jejunal pouch following total gastrectomy in 18 patients with cancer was reviewed. This technique results in a complete pouch and uses a double stapling technique with site-specific anastomosis between the oesophagus and pouch, in which a Hisoid angle is created.

Results There were no anastomotic leaks and pouch blood flow was within normal expected limits. Mean oesophageal pH above 7.0 for one 24-h period was 7.7 per cent. Emptying half-time was 67.8 min. After 2 years mean body-weight was 98.3 per cent of expected, mean food volume was 94.0 per cent of expected and mean meal frequency was 3.0 per day.

Conclusion This form of gastric reconstruction is an acceptable procedure which improves the quality of life in patients undergoing total gastrectomy.

The Roux-en-Y technique is commonly used to reconstruct the stomach after total gastrectomy. It is easy to perform and results in few postoperative complications. The problems associated with this technique, however, are decreased food volume, failure of digestive absorption with resultant malnutrition, and reflux oesophagitis. In an effort to overcome these problems a modification of an interpositioned, double jejunal, pouch design with site-specific anastomosis using a double stapling technique has been developed. This method delivers improved physiological results and reduced postoperative symptoms. This paper presents the technique and postoperative results.

Patients and methods

In the 3-year period from 1993 to 1996, reconstruction after total gastrectomy by the interposition of a double jejunal pouch using a double stapling technique was performed in 18 patients with resectable gastric cancer. Patients chosen had a life expectancy of more than 1 year after surgery and sufficient oesophagus and duodenum following resection of the tumour and margins. After a 3-week recovery period, patients were followed in the outpatient clinic. Patient characteristics are shown in Table 1.

Table 1 Details of 18 patients undergoing total gastrectomy with reconstruction by an interpositioned jejunal pouch

Sex ratio (F:M)	10:8
Mean (range) age (years)	54 (34–75)
Cancer stage*	
Ia	8
Ib	3
II	2
IIIa	1
IIIb	0
IVa	4
IVb	0

*Based on the criteria of the Japanese Research Society for Gastric Cancer¹

Reconstruction

Following total gastrectomy and lymph node dissection using the traditional procedures, the anvils of the Premium CEEA suture instrument (USSC, Connecticut, USA) are inserted into the edges of the oesophagus and duodenum. The small intestine is examined and a 30-cm segment of jejunum is selected that is approximately 20 cm distal to the ligament of Treitz to facilitate optimal blood supply.

The pouch is constructed with the GIA instrument (USSC). Roughly 20 cm of the oral end of segment is used to form the pouch. After two firings of the GIA, the incomplete pouch is inverted to make the final incision and to control bleeding from the mucosal side with sutures. The pouch is then completed, reinverted and passed underneath the transverse colon into position and ready for attachment. The free jejunal end is anastomosed to the duodenum using a double stapling technique with the 25-mm Premium CEEA instrument (Fig. 1a).

Next, the 25-mm centre gun is inserted through the pouch and out through the GIA staple line (Fig. 1b), at a point approximately 5 cm from the folded end of the pouch. The centre rod of the gun and anvil are connected and the oesophagus is attached to the pouch using the double stapling technique, and the entire instrument is removed once the anastomosis is complete. The GIA and Premium CEEA sites are closed with the 55-mm TA device (USSC).

Finally, the remaining ends of the jejunum are reanastomosed and the mesentery of the jejunum and transverse colon are closed (Fig. 1c). Note that approximately 1 cm of the GIA staple line can be seen on the proximal side of the oesophageal–jejunal anastomosis.

Follow-up

Heartburn, dumping symptoms, sensation of obstruction, regurgitant feelings, postprandial fullness and diarrhoea were recorded and scored. Diarrhoea was defined as more than three liquid stools per day for more than 3 days in a week. At 1 and 2 years after gastrectomy, patients were asked how many meals they ate in 1 day, body mass was measured, and food volume was compared to the preoperative volume. The complications of stenosis and leakage of anastomosis, regurgitant oesophagitis and dumping syndrome were recorded during follow-up.

Clinical examinations

At operation, blood flow of the pouch near the oesophageal anastomosis and normal jejunum was measured with a laser Doppler flowmeter (laser flowmeter ALF 21; Advance, Tokyo, Japan). After operation a nasogastric pH monitor (Digitrapper MK III; Synectics Medical, Stockholm, Sweden) was introduced into the abdominal oesophagus. Oesophageal pH was measured over a 24-h period, entered into a computer and the amount of time that the pH was above 7.0 (the alkaline regurgitant percentage) was calculated.

Also after operation, granulated resin labelled with indium-111 was added to a meal to evaluate pouch emptying time. Activity over the epigastrium, using a scintillation system, was viewed, counted and stored in a computer for later evaluation. A region of interest was drawn around the image of the jejunal loop and time-activity curves were generated over a period of time to calculate emptying half-times ($t_{1/2}$). After operation all patients

had a barium meal and endoscopy (GIF type XQ 230; Olympus, Tokyo, Japan).

Results

Survival

Of the 18 patients, 16 have survived and only two have died; of the two deaths, one patient died from disseminated disease and the other from perforation of the ileum.

Symptomatic assessment

The symptomatic assessment is shown in Table 2; a scoring system of 0–3 was used for each symptom. The most common complaint was nocturnal reflux which occurred in five patients, but only one of these had heartburn. This complaint was eliminated when patients did not lie down soon after a meal. Dumping was encountered in four patients. In all patients this symptom soon disappeared spontaneously. Two patients experienced dysphagia during a meal. One had stenosis of the anastomosis proximal to the oesophagus and required endoscopic dilatation. The other patient did not have stenosis and improved spontaneously. Postprandial fullness occurred in three patients. One patient suffered stenosis of the anastomosis distal to the duodenum, but improved after fibroscopic dilatation. In another case there was obstruction in the jejunum between the pouch and duodenum because of kinking, but the symptoms improved spontaneously. The other patient improved gradually. Diarrhoea occurred in one patient and was controlled successfully with medication. No evidence of anastomotic leakage was noted in any of the 18 patients.

Objective assessment

Assuming a preoperative body-weight and food volume of 100 per cent, measurements at 1- and 2-year periods after total gastrectomy were mean (s.e.m.) body-weight of 97.2(2.2) and 98.3(2.2) per cent respectively. Mean (s.e.m.) food volume was 75.0(6.9) per cent after 1 year and 94.0(7.5) per cent after 2 years. Mean (s.e.m.) meal frequency was 3.5(0.4) and 3.0(0.0) per day after 1- and 2-year intervals.

Clinical examination

Blood flow in the pouch during operation was within normal jejunal limits (Fig. 2). The mean (s.e.m.) oeso-

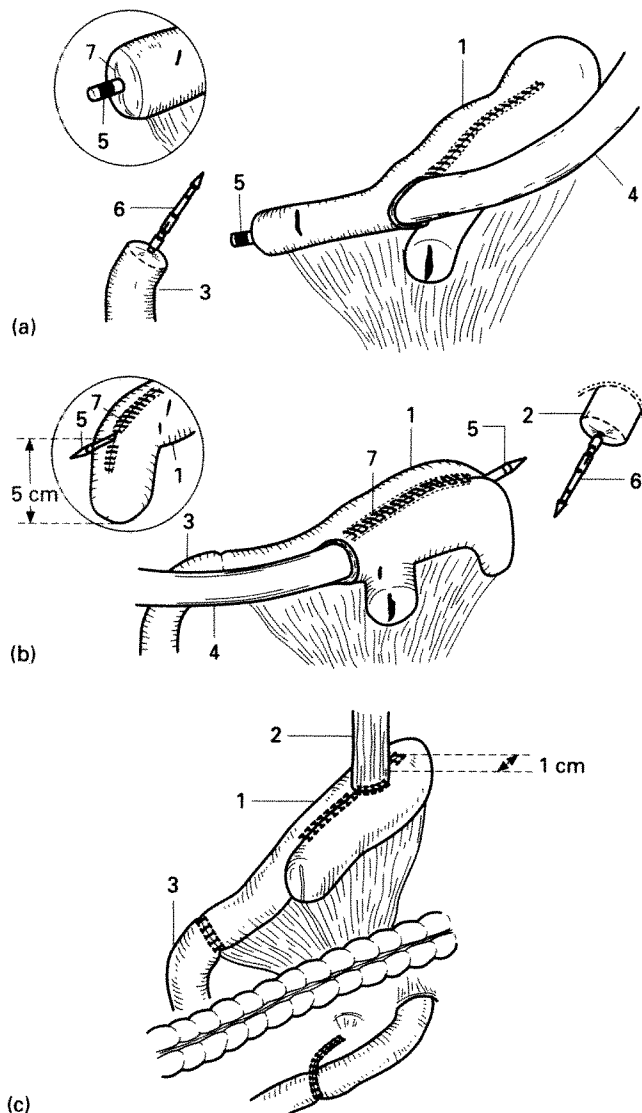


Fig. 1 a Connection of the free jejunal portion to the duodenum using the double stapling technique with the Premium CEEA. b Anastomosis of the pouch and oesophagus using the double stapling technique with the Premium CEEA. c Illustration of the complete reconstruction: 1, jejunal pouch; 2, oesophagus; 3, duodenum; 4, instrument of Premium CEEA; 5, centre rod of Premium CEEA; 6, anvil of Premium CEEA; 7, staple line of GIA

Table 2 Symptomatic assessment of 16 patients 5–32 months after total gastrectomy

Symptom	Score*			
	0	1	2	3
Heartburn	15	1	0	0
Dumping symptoms	12	4	0	0
Obstruction sensation	14	1	1	0
Regurgitant feeling	11	5	0	0
Postprandial fullness	13	1	2	0
Diarrhoea	15	1	0	0

*0, Absence of complaint; 1, mild; 2, moderate; 3, severe and persistent

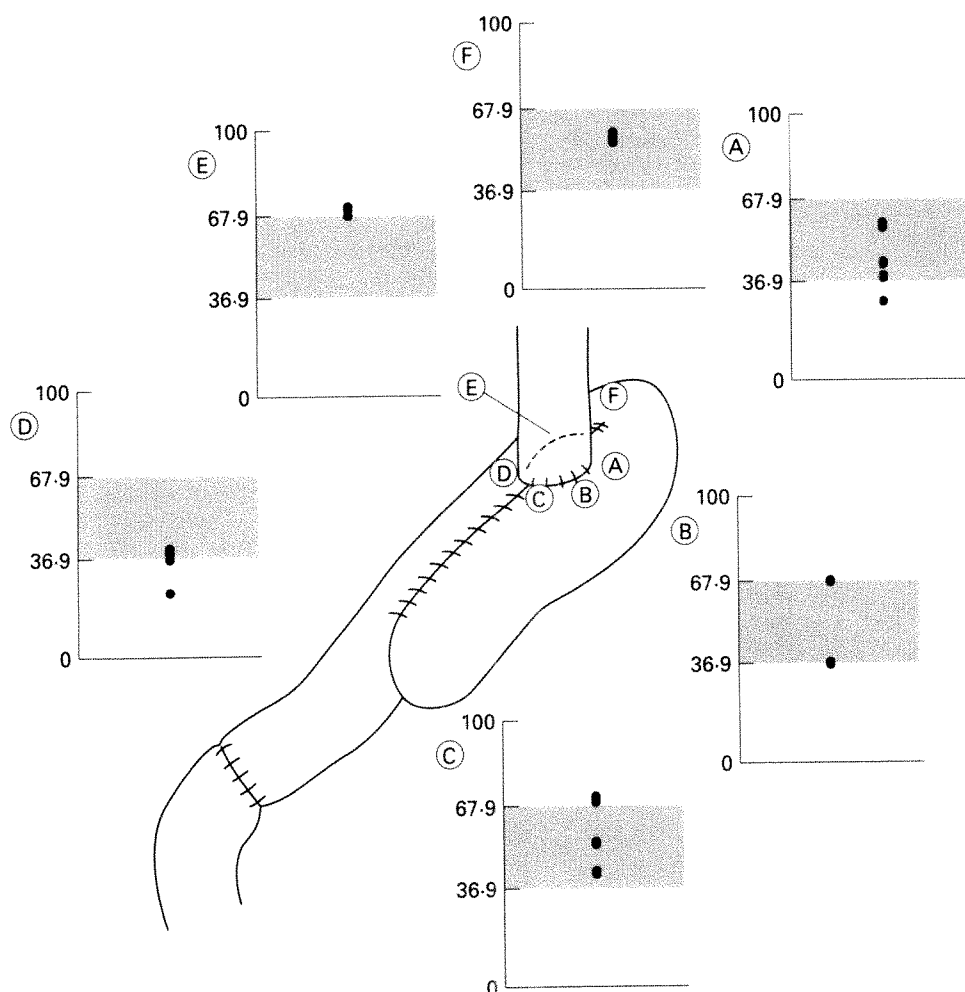


Fig. 2 Blood flow of the pouch near the oesophageal anastomosis (ml per min per 100 g) ($n = 4$). The normal blood flow range of the jejunum is shown by the shaded area ($n = 14$)

phageal pH percentage above 7.0 for one 24-h period was 7.7(2.6) per cent. This rate was 6.6(3.8) per cent during standing posture and 20.4(16.6) per cent while in the supine position. Mean(s.e.m.) $t_{1/2}$ for the pouch was 67.8(4.5) min and postoperative barium studies showed that the barium pooled in the pouch and then gradually flowed into the duodenum (Fig. 3). Fibreoptic endoscopes enter the duodenum easily and there is usually adequate space within the pouch and pseudofoirnx.

Discussion

The Roux-en-Y technique was, and is, frequently used for reconstruction after total gastrectomy. This method utilizes minimal anastomoses and results in few postoperative complications, such as leakage².

The duodenum and the first part of the jejunum have an important role in digestion and absorption. Unfortunately, following Roux-en-Y reconstruction, food passes only through the jejunum and not the duodenum, and poor absorption results in poor nutrition³⁻⁵. As it is important that food should pass through the duodenum and the first part of the jejunum, the present pouch reconstructive technique is better: these important areas of the

gastrointestinal tract remain coupled to maximize absorption and improve nutrition. Another advantage of the interpositional method is endoscopic accessibility to the duodenum and surrounding structures.

There are many opportunities to use the interpositioned double jejunal pouch design, which restores the original functions of storage and discharge of food to the intestine^{6,7}. To date, there is no established procedure for this operation because many types of reconstruction are in use. The technique has many anastomotic sites and, for that reason, it is potentially troublesome⁸. The present method of reconstruction safely achieves good nutritional status which is not inferior to that of the Roux-en-Y technique. This method does not appear to have a high anastomotic leak rate. After operation patients do not experience severe reflux oesophagitis or dumping syndrome. The main benefit of this technique is a more physiological reconstruction in which food passes through the duodenum, while maintaining the postoperative success of the Roux-en-Y technique.

Food volume was greater and gross body-weight frequently returned to normal after approximately 1 year with the interpositioned double jejunal pouch. The authors considered that the volume of the pouch should be taken into account in the design of the jejunal pouch.

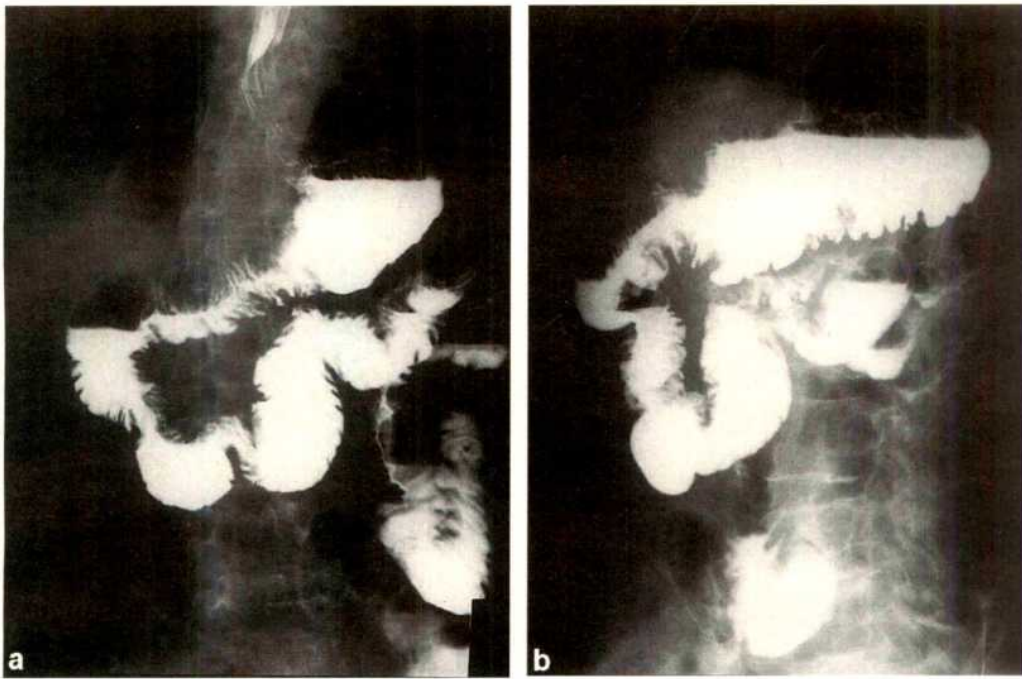


Fig. 3 Barium fluoroscopy following reconstruction. a Front view; b, side view

In some reconstructions, the pouch was made larger, proportional to body size; it then tolerated greater volumes, as expected. However, if the jejunal pouch was too large, it took longer to discharge food from the pouch and was not advantageous.

If the double jejunal pouch is constructed to be a complete pouch using the traditional technique, blood flow to the oesophageal anastomosis is reduced and leakage may ensue^{9,10}. If an incomplete pouch is constructed and the septum kept intact, the blood supply is improved and leakage minimized. Using this double stapling technique to connect the oesophagus to the double jejunal pouch, a complete pouch with near-normal capacity is produced. Blood flow to the pouch at the oesophagus is supplied through the double jejunal mesentery and is as good as normal jejunal blood flow. With this technique it is easy to insert the Premium CEEA into the pouch because it is a complete pouch lacking a septum. Normally difficulty is experienced with insertion in the traditional and Roux-en-Y techniques because of the narrow single jejunum design, despite using the smallest instrument, 25 mm in size, which is usually acceptable for a normal Japanese intestine. The double jejunal design facilitates easy insertion and anastomoses of the oesophagus. The stenosis rate was high (three of 18 patients), so the authors have considered using a larger Premium CEEA instrument than the oesophageal and jejunal sizes.

Some patients develop heartburn, but do not require treatment for reflux oesophagitis. pH monitoring reveals alkaline reflux to be minimal, possibly due to the angle created between the oesophagus and pouch. This new angle of His, when viewed endoscopically, appears to be similar to the original angle. This anastomosis is accomplished using the double stapling technique and is not placed behind the edge of the pouch, but on the front side.

Dumping syndrome is rare after this reconstruction because the pouch allows adequate storage function and the gradual passage of food to the duodenum¹¹. The

storage and discharge functions of the pouch are almost equivalent to those of a normal functioning stomach, because mean emptying $t_{1/2}$ is 67.8 min by scintigraphy. The poor discharge of the pouch and abdominal bulging that appears after a meal may be due to the disproportionate size of the pouch or an incorrect length of single jejunum. Based on experience, a 10-cm pouch and a 10-cm single jejunum are ideal, but must be modified to be proportional to the patient's size. Thorough follow-up for an extended period of time will be required to evaluate pouch changes over time.

The form of reconstruction presented here is a safe and preferable method for improving patients' quality of life after total gastrectomy.

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Tracheobronchial lesions following oesophagectomy: prevalence, predisposing factors and outcome

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Background Lesions of the trachea or main-stem bronchi with air leakage are a grave complication of oesophagectomy.

Methods Prevalence, predisposing factors and outcome of non-malignant lesions of the trachea or main-stem bronchi were analysed retrospectively in a consecutive series of 785 patients who had oesophagectomy for oesophageal cancer.

Results Overall 31 of 785 patients developed a tracheobronchial fistula 1–30 days after oesophagectomy. Based on the location of the lesions and clinical circumstances, the tracheobronchial fistulas were thought to be due to surgical injury (four patients), cuff pressure of the tracheostomy tube (two), local peritracheal infection resulting from a cervical anastomotic leak (seven) or 'ischaemia' after extensive peritracheal dissection (18). On multivariate analysis, transthoracic *en bloc* resection ($P < 0.01$) and preoperative radiochemotherapy for locally advanced tumours located at or above the level of the tracheal bifurcation ($P < 0.01$) predisposed to this complication.

Conclusion Non-malignant tracheobronchial lesions are a serious complication of transthoracic oesophagectomy with extensive lymph node dissection, particularly in patients undergoing preoperative radiochemotherapy for locally advanced tumours.

Tracheopleural or main-stem bronchopleural fistulas are grave complications of oesophagectomy because they frequently result in respiratory failure and death. Acquired non-malignant tracheobronchial lesions after oesophagectomy can occur as a consequence of intra-operative or postoperative trauma, leaks of the oesophagointestinal anastomosis with inflammatory involvement of the tracheobronchial tree, or ischaemia after extensive dissection in the upper mediastinum with devascularization of the trachea and main-stem bronchi^{1–7}. Traumatic injury to the trachea can occur during the surgical procedure or the process of endotracheal intubation, or as a consequence of the pressure exerted by the cuff of the endotracheal tube in patients requiring prolonged mechanical ventilation^{3,4,6,8}. These lesions are usually located in the proximal or middle part of the trachea. Peritracheal inflammation in patients with insufficiently drained oesophageal anastomotic leaks may also result in a fistula to the trachea^{3,9}. 'Ischaemic' lesions of the tracheobronchial tree become apparent several days after the surgical procedure and are usually located at or close to the tracheal bifurcation.

Despite the severity of this complication, literature on the prevalence, predisposing factors and outcome of tracheobronchial injuries after oesophageal resection is scant and comprises mostly case reports or descriptions of surgical techniques to close bronchial or tracheal leaks^{1–10}. An analysis was made of the prevalence, predisposing factors and outcome of non-malignant lesions of the trachea or main-stem bronchus in a consecutive series of 785 patients who had oesophagectomy for oesophageal cancer.

Patients and methods

Between July 1982 and October 1996, a total of 785 patients had an oesophageal resection for squamous cell carcinoma or adenocarcinoma of the oesophagus. The approach in all patients was to achieve complete tumour resection via either transmediastinal oesophagectomy (336 patients) or transthoracic *en bloc* resection (449). The choice of the procedure was based on location, histological tumour type, tumour stage and physiological status of the patient, as described previously^{11,12}. The tumour was located at or above the level of the tracheal bifurcation in 242 patients and below the level of the bifurcation in 543. A total of 172 patients who on preoperative staging had locally advanced tumours had preoperative chemotherapy ($n = 27$; cisplatin-based polychemotherapy) or combined preoperative radiochemotherapy ($n = 145$; 30–40 Gy radiation, 5-fluorouracil by continuous infusion with or without mitomycin) as described in detail elsewhere^{11–13}.

Before resection all patients had a thorough assessment of cardiopulmonary status, as well as of renal, hepatic and metabolic function. Use of a double-lumen endotracheal tube during resection was standard in those undergoing transthoracic surgery. A single-lumen tube was used in patients having transmediastinal resection. Between 1982 and 1992 transmediastinal resection was performed via a blunt transhiatal abdominocervical approach with blind dissection in the mediastinum. Since 1992 the transmediastinal dissection has been aided by a modified videomediastinoscope inserted from the cervical incision¹⁴. The transthoracic resection encompassed an *en bloc* resection of the primary tumour with extended mediastinal lymphadenectomy, i.e. *en bloc* removal of all peritumoral nodes, paraoesophageal nodes, subcarinal nodes, right and left peribronchial nodes, right paratracheal nodes and right recurrent nerve nodes^{11,15}.

Whole stomach or gastric tube interposition with a cervical oesophagogastrostomy was used for reconstruction whenever possible (707 patients). In the remainder a left colonic interposition with cervical oesophagocolostomy was used to reconstruct gastrointestinal tract continuity. The route of reconstruction was the posterior mediastinum in 501 patients.

The retrosternal route through the anterior mediastinum was chosen in 284 patients with locally advanced tumours in whom incomplete resection (R_1 or R_2) was thought possible by the surgeon performing the procedure. On histopathological assessment of the resected specimen, 308 patients had a locoregional tumour (pT_1 or pT_2 category) and 477 had a locally advanced tumour (pT_3 or pT_4 category). The indications for tracheostomy after surgical resection were pulmonary failure requiring prolonged mechanical ventilation (more than 3 days).

The present retrospective analysis is based on 31 of 785 patients who developed a tracheobronchial lesion with air leak 1–30 days after the surgical procedure. There were 25 men and six women of mean age 53 (range 40–71) years. Two patients in whom a lesion to the trachea or main-stem bronchus occurred during the surgical procedure, and was recognized and repaired immediately, are not included. Patients who developed a tracheobronchial fistula during the postoperative course due to infiltration by residual tumour are also not included.

The tracheobronchial lesion became apparent through a tracheomediastinal fistula in eight patients, a tracheopleural fistula in 19, and a fistula between the trachea and the interposed organ or oesophageal remnant in four. In all patients mechanical ventilation was required to control respiratory distress. To improve gas exchange, minimize air leakage and promote closure of the fistula, treatment with a high respiration rate and low tidal volume was employed in all patients^{16,17}. Airway toilette was achieved by frequent bronchoscopy (one to three times daily). Bronchoscopic fibrin gluing (15 patients), jet ventilation (six), airway stenting (12) and/or a covering of the tracheobronchial defect with a muscular pedicle flap (seven) were attempted in patients with an otherwise uncontrollable airway leak.

The prevalence of tracheobronchial lesions was compared between the various groups by means of univariate and multivariate analysis.

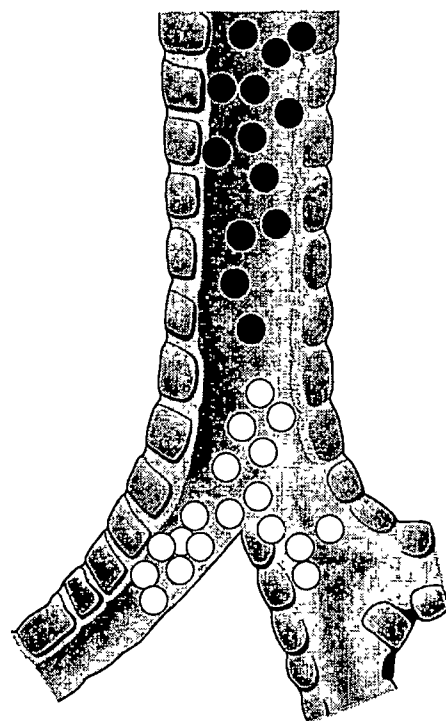


Fig. 1 Location of the tracheobronchial fistula in individual patients ●, fistula of 'non-ischaemic' origin; ○, fistula of 'ischaemic' origin

Results

Tracheobronchial lesions with air leak were observed in 31 of 785 patients who had oesophageal resection for cancer, accounting for an overall prevalence of 3.9 per cent. The time pattern of the appearance of the lesion and its location in individual patients are depicted in Figs 1 and 2. Based on the clinical circumstances and location of the airway fistula, the lesions were considered to be a consequence of surgical injury to the tracheobronchial tree which was not appreciated during the resection (four patients), to be due to cuff pressure from the tracheostomy tube in patients requiring prolonged positive-pressure ventilation because of postoperative pulmonary failure (two), to be caused by peritracheal inflammation resulting from an insufficiently drained cervical anastomotic leak (seven) or to result from ischaemia after extensive peritracheal and peribronchial dissection (18) (Figs 1 and 2).

Tracheobronchial lesions were more common in patients who had a transthoracic rather than a transmediastinal resection, in those with tumours located at or above, rather than below, the level of tracheal bifurcation, in patients who had reconstruction in the anterior rather than the posterior mediastinum, and in those who had preoperative neoadjuvant radiochemotherapy rather than preoperative chemotherapy or no preoperative therapy (Table 1). Multivariate analysis confirmed preoperative radiochemotherapy performed for locally advanced tumours at or above the level of the tracheal bifurcation ($P < 0.01$) and transthoracic *en bloc* resection with extended mediastinal lymphadenectomy ($P < 0.01$) as significant independent factors predisposing to postoperative tracheobronchial lesions. On multivariate analysis there was no relation between the size of the

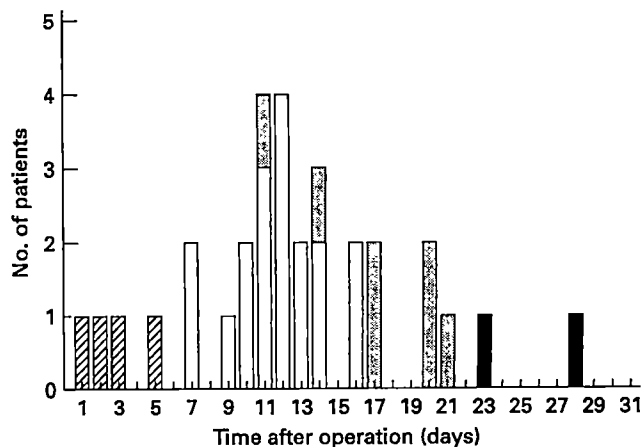


Fig. 2 Time of appearance of the tracheobronchial fistula in individual patients. ▨, Surgical injury; □, 'ischaemic'; □, inflammatory; ■, cuff pressure related

primary tumour (i.e. pT stage), tumour location, position of the interposed organ, age of the patient, and the presence of cardiovascular disease or diabetes with the rate of postoperative tracheobronchial lesions.

Ten of the 31 patients died during the postoperative course. The cause of death was respiratory failure in four patients, septic multiorgan failure in four and uncontrollable bleeding caused by septic erosion of the aorta in two. Each of these ten patients had transthoracic *en bloc* resection with extended mediastinal lymph-

Table 1 Prevalence of tracheobronchial lesions after oesophagectomy for oesophageal cancer in relation to type of resection, location of tumour, tumour stage, position of interposed organ and neoadjuvant therapy

Parameter	No. of patients	'Ischaemic' lesions	Surgical injury	Cuff pressure related	Inflammation	Overall prevalence
Type of resection						
Transthoracic	449	18 (4.0)	3 (0.7)	1 (0.2)	5 (1.1)	27 (6.0)
Transmediastinal	336	0 (0)	1 (0.3)	1 (0.3)	2 (0.6)	4 (1.2)
Tumour location						
At or above tracheal bifurcation	242	16 (6.6)	3 (1.2)	0 (0)	5 (2.1)	24 (9.9)
Below tracheal bifurcation	543	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)	7 (1.3)
pT category*						
pT ₁₋₂	308	4 (1.3)	2 (0.6)	2 (0.6)	3 (1.0)	11 (3.6)
pT ₃₋₄	477	14 (2.9)	2 (0.4)	0 (0)	4 (0.8)	20 (4.2)
Position of organ used for reconstruction						
Anterior mediastinum	284	12 (4.2)	2 (0.7)	1 (0.4)	3 (1.1)	18 (6.3)
Posterior mediastinum	501	6 (1.2)	2 (0.4)	1 (0.2)	4 (0.8)	13 (2.6)
Neoadjuvant therapy before resection						
Preoperative radiochemotherapy	145	11 (7.6)	0 (0)	0 (0)	4 (2.8)	15 (10.3)
Preoperative chemotherapy	27	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No preoperative therapy	613	7 (1.1)	4 (0.7)	2 (0.3)	3 (0.5)	16 (2.6)

*Pathological tumour (pT) category according to the Union Internacional Contra la Cancrum classification

adenectomy as the original procedure; eight had preoperative radiochemotherapy for a locally advanced tumour located at or above the level of the tracheal bifurcation. At the time of death, eight of the patients had a persistent airway fistula. When analysed according to the origin of the fistula, eight of 18 patients with a presumed ischaemic aetiology died during the post-operative course, compared with two of 13 with an alternative aetiology.

Discussion

Despite the close anatomical relationship between the trachea, main-stem bronchi and oesophagus, non-malignant tracheobronchial lesions are a rarely reported complication of oesophagectomy. In the present series tracheobronchial lesions after transmediastinal oesophagectomy were exceedingly uncommon, and in all instances were related to trauma or a cervical anastomotic leak, they were not infrequent after transthoracic resection and often presented as 'ischaemic' in origin.

The diagnosis and classification of tracheobronchial lesions as traumatic, cuff pressure related, or due to peritracheal inflammation is usually obvious from the clinical circumstances under which the lesion develops. These lesions can in most instances be prevented by subtle surgical technique, the use of low-pressure cuffs in those requiring prolonged mechanical ventilation, and effective drainage of oesophagointestinal anastomotic leaks. Consequently, these lesions are rare and, if they occur, can usually be managed successfully.

The situation is different for 'ischaemic' lesions. The classification of tracheobronchial lesions as ischaemic in origin was based on the time pattern of their occurrence (between days 7 and 17 after resection), their location at or close to the tracheal bifurcation, and the exclusion of other predisposing factors (e.g. cervical anastomotic leak or prolonged mechanical ventilation). This analysis shows that these lesions are related to preoperative radio-

chemotherapy and devascularization of the trachea and main-stem bronchi during extended mediastinal lymphadenectomy. Protective measures to prevent ischaemic tracheobronchial lesions include, in addition to careful dissection around the airway, preservation of the bronchial arteries during resection¹⁸. This approach, however, limits the radicality of the procedure, particularly in patients with tumours located at or above the level of tracheal bifurcation, whereas a significant effect on the prevalence of tracheobronchial lesions has so far not been demonstrated. In addition, preoperative radiochemotherapy with subsequent extensive resection in those who respond provides the only chance of cure in patients with locally advanced tumours at or above the level of the tracheal bifurcation¹³. Because of their pathogenesis and the unfavourable location at or close to the tracheal bifurcation, ischaemic lesions are also less amenable to therapeutic attempts than traumatic or cuff pressure-related lesions. This analysis shows that, despite aggressive intervention, the outcome of patients with ischaemic tracheobronchial lesions after neoadjuvant radiochemotherapy and extensive resection is markedly worse than that of those with 'non-ischaemic' lesions of the trachea.

A reduction of the air leak is essential to improve gas exchange and promote the closure of the fistula^{16,17}. This can be achieved best when the patient is breathing spontaneously. In patients requiring respiratory support, the intratracheal pressure should be reduced below the critical opening pressure of the fistula to minimize the air leak^{16,17}. Bronchoscopic fibrin gluing has been successfully used experimentally and clinically to seal bronchopleural fistulas or tracheobronchial anastomoses after pulmonary surgery^{19,20}. Fibrin sealing of tracheobronchial lesions after oesophagectomy in this series was helpful only in patients who did not require positive-pressure ventilation (i.e. those who were breathing spontaneously)²¹. Similarly, muscle flaps to cover the tracheobronchial defect have the highest chance for success in patients who breathe spontaneously²¹. Endotracheal and endobronchial stents

have recently been introduced and offer an attractive new option to treat tracheobronchial fistula^{22,23}. A prerequisite for the placement of an endotracheal stent is a sufficiently large margin proximal and distal to the lesion to anchor the stent. This may be difficult in patients with very proximal tracheal lesions or lesions in the left main-stem bronchus. Furthermore, clearance of bronchial secretions, mucostasis, formation of granulation tissue and migration of the stents are currently unsolved problems that limit the use of airway stents. Early recognition, reduction of the airway pressure, spontaneous breathing and aggressive surgical intervention whenever possible are therefore the key to the respiratory management of this grave complication.

In summary, the present report shows that patients receiving neoadjuvant radiochemotherapy for locally advanced oesophageal carcinoma located at or above the level of the tracheal bifurcation and who undergo subsequent transthoracic resection with extensive lymphadenectomy in the upper mediastinum have an increased risk of developing a non-malignant tracheo-bronchial fistula during the postoperative course. This appears to be related to the effects of radiation and surgical devascularization of the trachea and proximal main-stem bronchi, and is associated with a high post-operative mortality rate. Institutions employing multimodal concepts for the treatment of locally advanced tumours at or above the level of the tracheal bifurcation should be aware of this severe complication.

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Short note

Cholangitis in malignant biliary obstruction

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Cholangitis is a serious complication in malignant biliary obstruction. Bismuth *et al.*¹ implied that ampullary cancer frequently causes cholangitis. The aim of this retrospective study was to identify patients with malignant tumour causing biliary obstruction who are prone to cholangitis.

Patients and methods

One hundred and sixty-four patients with malignant biliary obstruction were admitted to this department from 1984 to 1995. There were 89 men and 75 women, of mean age 64 (range 31–82) years. They included 43 patients with hilar cholangiocarcinoma, 31 with gallbladder cancer, 30 with carcinoma of the common bile duct, 48 with pancreatic cancer and 12 with ampullary cancer. Primary tumour location was determined by preoperative imaging studies and/or pathological examination of the resected specimen. All patients underwent percutaneous biliary drainage. Aspirated bile was submitted for bacterial culture.

The diagnosis of cholangitis was made when a patient had fever, leucocytosis (10×10^9 per litre or more), hyperbilirubinaemia, positive bile culture, and/or right upper abdominal pain, without other septic complications. The incidence of cholangitis, either before or at the time of biliary drainage, was compared between the different types of malignancy. Fisher's exact test was used for data comparison

Results

Overall, eight (4.9 per cent) of the 164 patients developed cholangitis (Table 1). Five of the 12 patients with ampullary cancer developed cholangitis, while only three

(2.0 per cent) of the 152 with other malignant tumours developed cholangitis. The incidence of cholangitis in ampullary cancer was significantly higher than that in the other malignant neoplasms ($P < 0.0001$).

All three patients with non-ampullary malignant neoplasms and cholangitis also had a factor predisposing to bacterial proliferation, such as co-existing choledocholithiasis ($n = 2$) and endoscopic stenting before referral ($n = 1$), while none of the five with ampullary cancer had these factors.

The bacteria cultured from the bile were consistent with intestinal flora (Table 1).

Discussion

Malignant biliary obstruction is an infrequent cause of cholangitis^{1–3}. The overall incidence of cholangitis was 4.9 per cent in this series. The incidence was significantly higher in ampullary cancer. Bacteriological findings suggest that cholangitis may have resulted from reflux of intestinal flora through the ampulla. These results suggest that structural and functional destruction of the ampulla by cancer may cause ascending cholangitis.

Few patients with non-ampullary cancers developed cholangitis in this series. Concomitant conditions may have caused cholangitis in these patients^{2,3}. These results suggest that non-ampullary malignant neoplasms are only rarely complicated by cholangitis because the ampulla is intact.

In conclusion, among malignant pancreaticobiliary tumours causing biliary obstruction, ampullary cancer is more likely to develop ascending cholangitis because of ampullary destruction.

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Table 1 Characteristics of eight patients with cholangitis due to malignant biliary obstruction

Patient no.	Age (years)	Sex	Primary tumour location	Concomitant biliary complication	Bile culture results
1	52	F	Ampulla of Vater	None	<i>Enterococcus</i> sp.
2	72	F	Ampulla of Vater	None	<i>Klebsiella</i> sp.
3	53	M	Ampulla of Vater	None	<i>Enterococcus</i> sp.
4	80	F	Ampulla of Vater	None	<i>Escherichia coli</i> , <i>Klebsiella</i> sp., <i>Enterococcus</i> sp.
5	68	M	Ampulla of Vater	None	<i>Candida albicans</i>
6	72	M	Head of the pancreas	Cholecystocholedocholithiasis	<i>Enterococcus</i> sp., <i>Enterobacter</i> sp.
7	68	M	Head of the pancreas	Cholecystocholedocholithiasis	<i>E. coli</i> , <i>Enterococcus</i> sp., <i>Klebsiella</i> sp., <i>Morganella morganii</i>
8	49	M	Common hepatic duct	Endoscopic biliary drainage before referral	<i>Pseudomonas</i> sp., <i>Serratia marcescens</i>

Screening for gastric cancer by *Helicobacter pylori* serology: a retrospective study

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Background Screening by serology for *Helicobacter pylori* in young dyspeptic patients has been shown to be effective in reducing demand for endoscopy. *H. pylori* has been implicated in the causation of gastric cancer and the reported seropositivity rate in patients with gastric cancer ranges from 69 to 94 per cent. The aim of this study was to assess the potential value of *Helicobacter* antibodies as a method of selecting dyspeptic patients over the age of 45 years for endoscopy.

Methods A retrospective comparison of the antibody status to *H. pylori* was made between 154 patients with gastric cancer and a sex- and date of birth-matched dyspeptic control group. Results from the former group were correlated with demographic data and tumour characteristics.

Results Significantly more patients with gastric cancer were seropositive than controls (77 versus 66 per cent). *H. pylori* was not related to the Laurén classification of the tumour. Tumour site was significant: body and antrum tumours were associated with *Helicobacter* whereas cardiac tumours appeared to be unrelated.

Conclusion Screening by antibody assays to *H. pylori* would miss more than 30 per cent of current gastric cancers. The increasing incidence of cardiac cancer would cause this percentage to rise in the future.

Survival in gastric cancer depends on the extent of disease present at the time of diagnosis. The Japanese have shown 5-year survival rates of 95 per cent when the disease is confined to the mucosa and submucosa^{1–3}, rates that have been replicated in the UK and Europe^{4,5}. However, the 5-year survival rate in the UK as a whole is poor at between 5 and 11 per cent^{6–8}, with only 1 per cent of cases diagnosed as early gastric cancer^{4,9} and over 50 per cent being unsuitable for curative treatment^{6,7}. As a result, gastric cancer remains the fourth commonest cause of cancer death in the UK and the second commonest in the world¹⁰.

Helicobacter pylori infection has been shown to be strongly associated with the putative premalignant mucosal changes¹¹ of chronic atrophic gastritis^{12,13} and intestinal metaplasia¹⁴. Geographical studies have found that there is a good correlation between the rate of *H. pylori* seropositivity and gastric cancer rates^{15–17}. Retrospective case-control studies suggest that patients with gastric cancer are more likely to have been infected with *H. pylori* than controls and that they were more likely to have had higher titres of antibody to the microbe^{18,19}. Prospective studies have demonstrated that *H. pylori* infection is a risk factor for gastric carcinoma^{20–22} and suggest that up to 63 per cent of gastric cancers are caused by infection with *H. pylori*^{18–20}.

A policy of rapid investigation of all dyspeptic patients over the age of 40 years has increased the proportion of early gastric cancers from 2 to 15 per cent in a defined population⁴. This increases the demand for endoscopic services, although the 2–4 per cent yield of cancers²³ has

prompted attempts to develop methods of screening patients before endoscopy. *H. pylori* antibody testing has been used in those under 45 years of age; a policy of endoscopy only seropositive patients led to a reduction of 23 per cent in the total number of endoscopies performed whilst maintaining sensitivity for peptic ulcer of 97 per cent²⁴.

The reported seropositivity rate amongst differing worldwide populations with gastric cancer varied from 69 to 94 per cent^{18–21,25}. This study set out to determine the rate of seropositivity amongst a cohort of patients with gastric cancer to determine whether this could be a useful method for screening patients aged over 45 years before endoscopy.

Patients and methods

Serum samples were obtained from patients entered into the first two British Stomach Cancer Group studies of adjuvant chemotherapy^{26,27} for gastric adenocarcinoma. Samples were obtained at the time of entry into the studies and over the period of treatment. Samples were stored at –20°C. Data were available for prospectively collected records of demographic and clinicopathological information. Samples were available for 154 patients from the West Midlands Region. Seropositivity for *H. pylori* was determined by a commercial enzyme-linked immunosorbent assay (ELISA) Helico-G (Porton, Cambridge, UK). Serum samples were thawed and 30-μl aliquots assayed. A positive result was taken to be an antibody level of 8 units/ml or more.

Results were correlated with patient characteristics: age, sex, tumour stage, tumour histology and site of tumour. Stage was calculated by means of a clinicopathological system and histology was as defined by the Laurén classification, with independent assessment by two pathologists. The tumour site was classified into either cardia, body or antrum.

The control group consisted of dyspeptic patients recruited from *H. pylori* ELISA requests to the microbiology department at Queen Elizabeth Hospital, Birmingham, between 1994 and

1995, for whom the cause of dyspepsia was unknown. The study group was compared with the control group using a single control for each case, matched by sex and date of birth.

Data were analysed by the BMDP (Berkeley, California, USA) statistical software package. Exploratory data analysis was carried out to look for associations between *H. pylori* antibody status and patient characteristics. Comparisons were tested with the Pearson χ^2 test

Results

The patient characteristics of the 154 trial patients entered into the study are shown in Table 1. The median age of the population was 62 (range 29–74) years, with a male:female ratio of 3:1. There was no relationship between age and *H. pylori* antibodies; 72 per cent of patients aged 60 years or more were seropositive for *Helicobacter*, as were 83 per cent of those under 60 years of age. There were more men with carcinoma than women, but the difference in the proportion of each sex positive for *H. pylori* (men 74 per cent, women 85 per cent) was not significant.

The majority of patients presented with stage III disease (58 per cent); 25 per cent had stage I or II disease and 17 per cent stage IV. There was no association between stage at presentation and *H. pylori* status. Of intestinal-type tumours, 76 per cent were seropositive for *H. pylori* compared with 78 per cent of diffuse-type

Table 2 *Helicobacter pylori* antibody status in non-cardial tumours and controls

	Non-cardial tumours	Controls
ELISA positive	62 (85)	102 (66)
ELISA negative	11 (15)	52 (34)
Total	73 (100)	154 (100)

Values in parentheses are percentages. ELISA, enzyme-linked immunosorbent assay. $P=0.003$ (non-cardial tumours versus controls, χ^2 test)

Table 3 *Helicobacter pylori* antibody status in cardiac tumours and controls

	Cardial tumours	Controls
ELISA positive	5 (38)	102 (66)
ELISA negative	8 (62)	52 (34)
Total	13 (100)	154 (100)

Values in parentheses are percentages. ELISA, enzyme-linked immunosorbent assay. $P=0.045$ (cardial tumours versus controls, χ^2 test)

Table 1 Characteristics of the 154 trial patients

Factor	No. of patients	ELISA positive	χ^2	P
Sex				
M	115	85 (74)	1.86	0.17
F	39	33 (85)		
Age (years)				
<60	60	50 (83)	0.006	0.94
≥60	94	68 (72)		
Stage				
I	13	10 (77)	2.67	0.26*
II	26	22 (85)		
III	89	64 (72)		
IV	26	22 (85)		
Site				
Antrum	55	45 (82)	5.42	0.07
Body	18	17 (94)		
Cardia	13	5 (38)		
Other†	65			
Histology				
Well or moderate	47	36 (77)	2.59	0.11
Poor or anaplastic	60	53 (88)		
Signet†	8			
Squamous†	2			
Unknown†	37			
Laurén classification				
Intestinal	75	57 (76)	0.49	0.78
Diffuse	37	29 (78)		
Mixed†	13			
Unknown†	29			

Values in parentheses are percentages. *Stages I and II were combined to allow adequate numbers for analysis; †not used in data analysis. ELISA, enzyme-linked immunosorbent assay

tumours (P not significant). The incidence of *H. pylori* antibodies was higher in patients with gastric cancer than in those with dyspepsia: 118 cases (77 per cent) were seropositive for *H. pylori* compared with 102 controls (66 per cent) ($P=0.04$).

Comparison between the three sites failed to show a significant association between *H. pylori* antibody status and site ($P=0.07$). However, when cardiac and non-cardiac (antrum and body) tumours were compared, non-cardiac tumours had a significantly higher association with *H. pylori* antibody status ($P=0.046$). Comparing non-cardiac tumours with the control group, 85 per cent of cases were seropositive compared with 66 per cent of controls ($P=0.003$) (Table 2). For the cardiac tumours, only five (38 per cent) of 13 cases were seropositive compared with 66 per cent of controls; this is of borderline significance ($P=0.045$) (Table 3).

In the control group there was no decrease in the rate of *H. pylori* infection with more recent birth dates ($P=0.39$). A higher proportion of men was seropositive for *Helicobacter* than of women (70 versus 54 per cent respectively) but this was not significant ($P=0.06$).

Discussion

Prompt investigation of every new dyspeptic patient over the age of 40 years presenting to their general practitioner has been shown to influence the proportion of early and operable cases of gastric cancer. The yield of such an approach is around three gastro-oesophageal cancers per

100 endoscopies, and this has focused attention on methods of selecting patients for investigation. The epidemiological data on the association between gastric cancer and *H. pylori* infection have been used to suggest a causative link. This would suggest that screening patients for evidence of *H. pylori* infection might be a useful method for identifying patients at increased risk.

There are problems inherent in the use of an ELISA as a method to determine *H. pylori* infection. It has been shown that Western blotting will suggest previous infection in patients negative on ELISA testing²⁵, while strain heterogeneity might increase the risk of false-negative findings²⁸. In comparison with histology and breath testing, Helico-G has a sensitivity for active infection of 96 per cent and provides the best currently available method for assessing infection in large groups.

To use a test as a method of selection for investigation, it must pick up disease at an early stage, select a group with a significant risk, and identify most of those with the disease. The present study has attempted to address the last two points. In the condition of interest, early gastric cancer, studies are available that show a high incidence of infection (77–93 per cent)^{29,30}. The incidence of *H. pylori* in the dyspeptic control group would allow a reduction in the rate of endoscopy by one-third. However, only 77 per cent of all cancers and 38 per cent (five of 13) of cardiac cancers were antibody positive. While the overall incidence of gastric cancer is reported to be declining, that of cardiac cancer is rising rapidly, from 7 per cent in 1961 to 35 per cent in 1981 in the West Midlands.

The association between gastric cancer and *H. pylori* infection has led to a re-examination of the process of gastric carcinogenesis. Infection is thought to be acquired early in life with rising rates of infection with increasing age believed to be the result of a cohort effect. This was not demonstrated in the present study. The Correa model has been the basis for development of intestinal-type cancer, which is commonly found in areas with the highest incidence of gastric cancer. This model suggests a progression through gastritis and atrophy to intestinal metaplasia, and *H. pylori* has been strongly implicated in the development of these changes^{12–14}. This would suggest a greater association between *H. pylori* infection and intestinal-type cancer than with diffuse-type cancer. The present study supports other work that has failed to find this difference^{18,19,21,22,29}. It has been proposed that this anomaly occurs as a result of the timing of carcinogenesis, the diffuse type arising during the inflammatory stage²² whereas the intestinal-type tumours develop from the later changes of atrophy and metaplasia.

This study shows an association between evidence of *H. pylori* infection and non-cardial gastric cancer (odds ratio 2.87 (95 per cent confidence interval (c.i.) 1.39–4.00)), while for the 13 cardiac tumours 28 per cent fewer cases were positive compared with controls (odds ratio 0.32 (95 per cent c.i. 0.10–1.02)). There is no consensus on the association between *H. pylori* infection and cardiac cancer. Of the series with more than ten cardiac cancers, a UK study with 18 cases found no difference in the relationship between *H. pylori* infection and cardiac and non-cardiac tumours²⁵, whereas a Swedish study with 19 cases agreed with the present findings²¹. The relationship between *H. pylori* infection and cardiac tumours needs to be evaluated further, but this difference is in keeping with the evolving pattern of gastric cancer in the Western world suggesting differing aetiologies. Epidemiological studies confirm that tumours of the cardia appear more akin to cancers of the

oesophagus than to the more distal tumours of the stomach³¹.

The results of this study show that *H. pylori* antibody screening is unsuitable for use as a method of pre-endoscopy screening of older patients. Although there would be a reduction in the number of endoscopies, this would be at the cost of missing over 30 per cent of the cancers assuming current site distribution, this figure rising further with the increasing frequency of cardiac cancers. Screening based on serology to *H. pylori*, regardless of any future increases in sensitivity, cannot be implemented. Patients over the age of 45 years with dyspepsia require endoscopy to exclude malignancy.

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Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland Abstracts

The following abstracts were presented at the Scientific Meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. The meeting was

held on 25-26 September 1997 at the Village Hotel, Headingley, Leeds, UK.

Laparoscopic common bile duct exploration

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Background The usefulness of laparoscopic bile duct exploration was evaluated

Methods From August 1991 to February 1997, the outcome of 300 laparoscopic common bile duct explorations has been evaluated. The last 200 explorations were followed prospectively. Transcystic exploration was performed in 171 patients and in three of these an antegrade stent was inserted. Laparoscopic choledochotomy was performed in the remaining 129 patients. Of these, 40 had primary closure alone, 13 underwent primary closure over a stent, 61 had a T tube inserted and 11 underwent laparoscopic choledochoduodenostomy.

Results The median age of the patients was 56 (range 19-100) years, the operating time 95 (range 35-300) min and postoperative stay was 3 (range 1-35) days. There were eight negative explorations. Twelve patients underwent conversion to open operation. Postoperative endoscopic retrograde cholangiography (ERC) was used in 21 patients for clinical suspicion of retained stones and nine had common bile duct stones at ERC. Ten patients required reoperation. There was one postoperative death and major morbidity in 22 patients (7 per cent).

Conclusion Laparoscopic transcystic basket extraction of common bile duct stones under fluoroscopic guidance is a relatively quick, successful and safe technique. Choledochotomy, when required, is associated with a higher morbidity, particularly with T tube insertion, and primary bile duct closure with or without insertion of a biliary drains stent is a more satisfactory technique for both surgeon and patient. The potential for the majority of patients with gallbladder and common duct calculi to expect a curative one-stage laparoscopic procedure without the need for external biliary drains can now be achieved with lower morbidity and mortality rates than ERC and endoscopic sphincterotomy alone.

Gadolinium-enhanced magnetic resonance imaging in the assessment of pancreatic cancer

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Background Magnetic resonance imaging (MRI) has had limited evaluation in the preoperative assessment of the resectability of pancreatic cancer. The aim of this study was to examine the usefulness of gadolinium-enhanced MRI alone in determining the resectability of pancreatic cancer.

Methods Twenty-three patients with pancreatic carcinoma (21 ductal and two ampullary tumours) underwent gadolinium-enhanced MRI before surgical staging. The images were reported by a single consultant radiologist. The images were classified as showing irresectable disease if there was any of the following: (1) encasement, invasion or obstruction of the major vessels; (2) extension beyond the pancreatic fascia; or (3) nodal, peritoneal or liver metastases.

Results Of 23 patients, six had histologically proven liver or peritoneal metastases found at laparoscopy. Seventeen patients had a laparotomy with seven undergoing resection of the tumour. Nine MRI scans were classified as showing resectable and 14 as irresectable disease. The sensitivity and specificity of

MRI to determine resectability were 86 and 81 per cent respectively. The positive predictive value of resectability was 67 per cent and the negative predictive value was 93 per cent. In three patients the disease was classified as resectable by MRI but resection was not performed. All had lymph node metastases. There was concordance in determining vascular involvement between MRI and findings at operation in all except one patient, who had hepatic artery invasion. One patient had a hepatic metastasis diagnosed by MRI which was found to be a haemangioma at operation.

Conclusion MRI performs well in assessing the overall resectability of pancreatic carcinoma but is not reliable at detecting lymph node metastases.

Laparoscopy and laparoscopic ultrasonography in upper gastrointestinal cancer: do they improve staging?

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Background The staging modalities currently available for upper gastrointestinal cancer (tumours of the oesophagus, stomach and pancreas) have significant limitations, inaccurate staging and inappropriate management decisions are not uncommon. In this study the value of laparoscopy and laparoscopic ultrasonography in the preoperative staging of upper gastrointestinal tumours was assessed.

Methods Between August 1994 and January 1997, 76 patients with gastrointestinal cancer (48 men; mean age 69 (range 49-87) years) underwent either laparoscopy alone (gastric cancer, 34; lower oesophageal cancer, four; pancreatic cancer, one) or laparoscopic ultrasonography (gastric cancer, 20; lower oesophageal cancer, eight; pancreatic cancer, nine) in addition to conventional imaging (computed tomography and/or ultrasonography) for preoperative staging purposes.

Results Laparoscopy alone provided additional information compared with conventional imaging in 17 of 39 patients. These additional findings included peritoneal deposits ($n=8$), small amounts of malignant ascites ($n=5$) and liver metastases ($n=1$). Three patients were downstaged and subsequently underwent a successful resection. Laparoscopic ultrasonography supplied additional information in 13 of 37 patients compared with conventional imaging, resulting in a change of management. The additional findings included portal vein invasion ($n=3$) and liver metastases ($n=3$). There were no complications related to laparoscopy or laparoscopic ultrasonography.

Conclusion In this pilot study laparoscopy and laparoscopic ultrasonography significantly improved staging in upper gastrointestinal cancer compared with conventional imaging. This has important implications with regard to patient management and counselling.

Training in hepatopancreatobiliary surgery

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Background This paper analyses the early outcome of patients undergoing major hepatopancreatobiliary resection in a single specialist unit, with regard to the grade of the surgeon performing the operation.

Methods Over a period of 29 months (January 1994 to May 1996), details of 112 patients who underwent either pancreatic or liver resection, for both benign and malignant disease, were collected prospectively.

Results Overall, 19 (31 per cent) of 62 patients who had pancreatic resection and 21 (42 per cent) of 50 patients who underwent liver resection were operated on by trainees under consultant supervision. Fourteen of the 40 pancreatoduodenectomies and five of 19 distal pancreatectomies were done by trainees under supervision, while all three total pancreatectomies were done by a consultant. Fifteen of 36 right hepatectomies and six of 12 left hepatectomies were done by trainees under supervision, while two atypical resections were done by a consultant. In the 43 pancreatic resections done by consultants there were eight anastomotic leaks and one death, and in the 19 pancreatic resections done by the trainees there were two anastomotic leaks and no deaths. In the 29 liver resections done by consultants there were four leaks and no deaths, and in the 21 liver resections performed by trainees there were two leaks and no deaths. The other surgical and non-surgical complications were comparable.

Conclusion This series has demonstrated that in a unit with a major interest in hepatopancreatobiliary surgery there appears to be no difference between a consultant and a supervised trainee in the early outcome following major resection. There is no reason why these results cannot be duplicated in all specialist units and the results demonstrate the potential training opportunities that can be provided by subspecialization in general surgery.

Site and histological type of oesophageal and gastric cancer: retrospective population-based case-note survey of over 1000 cases

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Background The precise site and extent of oesophageal and gastric cancers were defined in a population-based study, in order to clarify the perception of a change in the site and histological type of these tumours. Furthermore, an inclusive system for recording site, which allows for the fact that tumours involve more than one subsite in the oesophagus and stomach, was developed.

Methods Some 1400 cases of cancer of the oesophagus or stomach were identified from records of the North Western Regional Cancer Registry, which catered for a population of 4 030 800 in 1993. Case-note review of 1255 cases was carried out. Some 188 patients were excluded from further analysis because following review of the case notes they did not have invasive oesophageal or gastric cancer diagnosed in 1993. In the remaining 1067 (627 men, 440 women), tumour site was recorded from endoscopic, radiological, operative and pathological details. An inclusive hierarchy for recording site was used.

Results

Site of tumour	Men (n = 627)	Women (n = 440)
Encroaching on cardia, OGJ or lower oesophagus	396 (63.2)	237 (53.9)
Oesophagus, other site	44 (7.0)	58 (13.2)
Stomach, other site	187 (29.8)	145 (33.0)

Values in parentheses are percentages. OGJ, oesophagogastric junction

There was a male:female ratio of 2.3:1 for tumours involving the OGJ, whereas tumours confined to oesophagus and stomach

had ratios of 1:1 and 1.3:1 respectively. Adenocarcinoma of the oesophagus and OGJ outnumbered squamous carcinoma by 5:1 in men and 1.3:1 in women.

Conclusion Over 60 per cent of upper gastrointestinal cancers in men and 50 per cent of those in women involve the cardia, OGJ or lower oesophagus. Surgeons who treat these cancers need both thoracic and abdominal training and experience.

Multidisciplinary approach to the management of oesophagogastric carcinoma: an early experience

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Background Traditionally the treatment of patients with oesophagogastric cancer has been influenced by the referral route. For patients with similarly staged disease a surgeon would operate, a gastroenterologist intubate and an oncologist treat with chemoradiation. This situation is unsatisfactory.

Methods From May to November 1995 the treatment and survival of new patients with oesophagogastric cancer in a single county were audited (62 patients; 24 with oesophageal cancer and 38 with gastric cancer). A multidisciplinary team was established in November 95 to coordinate treatment of future patients according to agreed protocols. Data have been collected prospectively during the past 17 months on 73 patients, 43 with oesophageal cancer and 30 with gastric cancer (study group), and the results compared with those of the earlier audit. The protocol for patients with oesophageal cancer comprised surgery for physiologically fit patients with limited disease, remaining patients were palliated by radiotherapy or intubation. Fit patients were aged less than 75 years with normal echocardiographic findings and forced expiratory volume in 1 s above 1.25 litres. Staging was by chest radiography, abdominothoracic computed tomography and endoscopic ultrasonography. Patients staged T₁T₂N₀ had immediate surgery and those staged T₃ or N₁ had preoperative chemoradiotherapy. Treatment for gastric cancer was primarily by surgery with D₂ gastrectomy for cure and D₁ or bypass for palliation. D₂ gastrectomy was performed in fit patients aged 80 years or less staged T₁N₁ or lower.

Results

	Oesophageal cancer		Gastric cancer	
	Audit (n = 24)	Study (n = 43)	Audit (n = 38)	Study (n = 30)
Surgery	8 of 24	17 of 43	24 of 38	24 of 30
Preoperative chemoradiotherapy	0 of 8	10 of 17*	2 of 24	2 of 24
Resection	6 of 24	17 of 43	20 of 38	21 of 24†
Open and close	2 of 8	0 of 17	4 of 24	3 of 24
6-month survival	11 of 24	18 of 31	22 of 36	15 of 21

* $P < 0.05$. †For patients in the audit group who had definitive surgery all had D₁ resection or bypass, while in the study group eight had D₂ resection, 12 D₁ and one a bypass ($P < 0.01$). Intubation rates for oesophageal carcinoma were similar for both groups.

Conclusion The introduction of a team approach to patients with oesophagogastric cancer has allowed accurate disease staging and consistency in patient management. There has been a modest improvement in survival at 6 months of 10 per cent for both oesophageal and gastric cancer. More patients with oesophageal cancer are being referred for neoadjuvant therapy and more patients with gastric cancer are undergoing surgery, in particular D₂ resection.

Role of the oesophagoprobe in the staging of oesophageal carcinoma

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Background Locoregional staging of patients with oesophageal carcinoma by endoscopic ultrasonography using the 14-mm echoendoscope is impeded by an inability to negotiate malignant stricturing in up to 30 per cent of patients. Moreover, it is considered that significant luminal stenosis equates with advanced disease. An initial experience with the new Olympus MH-908 oesophagoprobe is presented.

Methods The 8-mm oesophagoprobe scans at a frequency of 7.5 MHz and is introduced over a preplaced guidewire. Staging is performed as an outpatient procedure under intravenous midazolam sedation. Selection for its use in preference to the larger 14-mm echoendoscope is based on the initial gastroscopy findings.

Results Over a 12-month period 38 patients with oesophageal carcinoma (adenocarcinoma, 28; squamous carcinoma, ten) were staged with the 8-mm scope. The median age of the 15 women and 23 men was 67 (range 34–82) years. Full locoregional staging was achieved in every patient. The procedure was well tolerated and there were no complications. Prior dilatation was required in eight patients, to 9 mm ($n=2$), 11 mm ($n=5$) and 14 mm ($n=1$). The Table shows the correlation between circumferential tumour extent and endoscopic ultrasonographic T and N stage.

Circumference	Stage					
	T ₁	T ₂	T ₃	T ₄	N ₀	N ₁
<100 per cent ($n=14$)	1	1	12	0	1	13
100 per cent ($n=24$)	0	3	18	3	4	20

There was no significant difference in T or N stage between the two groups (less than 100 per cent *versus* 100 per cent circumferentiality). To date 17 patients have undergone surgical resection. Histological correlation revealed an accuracy of 88 per cent (15 of 17 patients) for T stage and 76 per cent (13 of 17 patients) for N stage. The sensitivity and specificity for malignant lymphadenopathy, as defined by the criteria of spherical shape, distinct border, heterogeneous areas within the nodes and a diameter of 6 mm or more, were 90 and 57 per cent respectively. **Conclusion** The 8-mm oesophagoprobe can safely and accurately stage patients with oesophageal carcinoma. These findings indicate that severe luminal stenosis is not always synonymous with advanced disease.

Role of endoscopic ultrasonography in the assessment of upper gastrointestinal pathology

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Background The clinical impact of endoscopic ultrasonography (EUS) on the investigation of upper gastrointestinal disease was evaluated.

Methods The records of all patients who had undergone EUS for the investigation of upper gastrointestinal pathology over the past 4 years were examined. The EUS findings were compared with those of other imaging investigations, operative findings and histology when available. The sensitivity and specificity of EUS for the assessment of various pathologies were calculated. Changes in management as a result of EUS were noted.

Results Five hundred and forty-six patients underwent EUS for investigation of oesophageal, gastric and pancreatobiliary disease. Principal indications for the procedure were locoregional staging of cancer ($n=313$), the investigation of submucosal lesions seen at endoscopy ($n=34$) and assessment of the bile duct before laparoscopic cholecystectomy ($n=60$). EUS accurately predicted tumour and node status in oesophageal

cancer (accuracy 92 and 86 per cent respectively). It identified T₄ tumours with greater accuracy than computed tomography and is now used routinely to select patients for non-surgical therapy. EUS had a sensitivity and specificity of 88 and 96 per cent respectively in the assessment of choledocholithiasis. It has now replaced diagnostic endoscopic retrograde cholangiopancreatography in selected patients. EUS correctly diagnosed submucosal lesions identified at endoscopy in 66 per cent and guided biopsy in a further 10 per cent. EUS was of no value in staging large pancreatic tumours but identified otherwise unsuspected vascular invasion in several patients and clearly imaged small pancreatic tumours not visualized with other techniques.

Conclusion EUS is highly accurate in the assessment of a variety of upper gastrointestinal diseases and, when used appropriately, can have a significant impact on patient management.

Management of acute pancreatitis in a district general hospital

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Background The effect of defined management algorithms on the outcome of patients with acute pancreatitis in a district general hospital (DGH) was assessed prospectively.

Methods Data were collected prospectively over the period 1991–1995 for all patients diagnosed as having acute pancreatitis. Patients were managed according to agreed protocols which included (1) early endoscopic retrograde cholangiopancreatography for gallstone pancreatitis, (2) definitive treatment for gallstone pancreatitis within the initial admission as endoscopic sphincterotomy alone for elderly patients or cholecystectomy for fit patients without duct calculi and (3) management of severe acute pancreatitis by the upper gastrointestinal surgeon.

Results Two hundred and twenty patients (median age 64 (range 10–98) years) were admitted on 308 occasions with acute pancreatitis secondary to gallstones (113), alcohol (32) or other factors (75). The in-hospital and 28-day mortality rate was 7.3 per cent. Eleven of these 16 deaths occurred in patients aged 80 years or over. Median length of hospital stay was 8 (range 1–75) days. Twenty patients spent a median of 6 (range 1–52) days in intensive care. Twelve patients underwent 16 separate surgical procedures including necrosectomy, pancreatic resection and packing of 'open abdomen'. Eight of these 12 surgically treated patients survived.

Conclusion These mortality rates compare favourably with the 6–20 per cent rate reported in the literature and suggest that good results can be achieved in the DGH setting when common policies are accepted by all general surgeons and severe pancreatitis is managed by a committed upper gastrointestinal surgical team.

What is an upper gastrointestinal surgeon?

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Background The workload implications of upper gastrointestinal subspecialization in a district general hospital (DGH) were assessed.

Methods Data have been collected prospectively over a 12-month period (March 1996 to February 1997) in this hospital, which serves a population of 320 000. In this DGH all upper gastrointestinal malignancy, biliary obstruction and severe acute pancreatitis is managed by one of five general surgeons.

Results Major upper gastrointestinal surgery included oesophageal resection ($n=10$), gastric resection ($n=8$), major pancreatic surgery ($n=8$) and antireflux surgery ($n=5$). The upper gastrointestinal surgeon also performed 85 of 155 laparoscopic cholecystectomies, 164 of 250 endoscopic retrograde cholangiopancreatographies and all endoscopic procedures for the palliation of unresected oesophageal tumours; was responsible

for the management of all patients with severe pancreatitis; and performed 51 colorectal operations over the 12 months studied.

Conclusion Successful management of the severely ill patient with upper gastrointestinal disease requires consultant supervision on a day to day basis throughout the year. If such upper gastrointestinal disease is to be managed in a DGH, two surgeons with upper gastrointestinal experience will be required if high-quality care and reasonable working conditions are to be achieved. Since the elective workload of upper gastrointestinal surgery is insufficient to occupy two surgeons fully, they will continue to perform other gastrointestinal surgery including colorectal resections. Both the Association of Upper Gastrointestinal Surgeons and Association of Coloproctology of Great Britain and Ireland need to represent those working in a DGH as well as the 'tertiary referral specialist'.

Endoscopic ultrasonography in staging of tumours of the oesophagus and gastro-oesophageal junction

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Background Modern management of oesophageal cancer demands accurate preoperative staging and whilst computed tomography (CT) is probably entirely adequate for the assessment of distant metastases it has major limitations in local staging of the tumour. Endoscopic ultrasonography (EUS) is the only staging modality that demonstrates the layers of the gut wall and is therefore ideally suited for staging upper gastrointestinal tract tumours.

Methods The EUS and clinical records of all patients undergoing the procedure as a staging assessment for either an oesophageal or a gastro-oesophageal junction tumour between the first EUS examination in July 1995 and December 1996 were reviewed. All examinations were performed using the Olympus UM20 Echo-endoscope (Olympus; Keymed, Southend, UK). The ultrasonographic extent of the tumour was classified according to the tumour node metastasis (TNM) classification of the Union International Contra la Cancrum (third edition, second revision 1992). In patients with a malignant stricture through which the endoscope would not pass, the proximal margin of the tumour was scanned. Surgery was performed within 4 weeks of EUS. The sonographic findings were correlated with the pathology of the resected specimen which was also staged according to the TNM classification.

Results There were 39 patients (25 men) studied, with a mean age of 66 (range 43–78) years. These patients represented 40 per cent of all patients with tumours of the oesophagus and gastro-oesophageal junction seen in this unit. The remaining 60 per cent were either not considered for staging because of age/general medical condition or had CT showing metastatic disease. Of the 39 patients there were three failed examinations. Ten patients did not go on to surgery (in six EUS showed inoperable disease, one had cancer of the bronchus, three by patient/clinician choice). In the 26 patients in whom pathological correlation was available, the overall accuracy for T staging was 84 per cent, with understaging in 12 per cent and overstaging in 4 per cent. The overall accuracy for N staging was 58 per cent (understaging 27 per cent, overstaging 15 per cent). If a similar correlation was limited to the last 6 months of the study the T staging accuracy improved to 100 per cent and the N staging accuracy to 70 per cent.

Conclusion This experience with EUS confirms reports of other workers around the world, who have shown that this is an appropriate modality for the local staging of oesophageal cancer and, in particular, after the operators have been through a reasonable learning curve, accuracies approaching 100 per cent are easily attainable for T staging; unfortunately results for N staging have not been so impressive. Other workers have encountered similar problems, although some have managed to produce better results. EUS constitutes a major advance in the local staging of tumours of the oesophagus and gastro-oesophageal junction and it is hoped that this improved staging

information will in turn result in a meaningful advance in the management of these tumours.

Upper gastrointestinal cancer in general surgery at a district general hospital

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Background The recommended workload for a standard surgical team has been clearly defined by the Royal College of Surgeons. The annual outpatient workload should consist of approximately 1000 new patients and the annual operative workload should be 900 intermediate equivalents. The volume of work generated by one consultant (of a surgical unit of seven) undertaking all the upper gastrointestinal cancer work in a district general hospital in South Wales serving a population of 440 000 was assessed.

Methods One year's elective workload was audited prospectively and the volume of outpatient and inpatient workload assessed with particular reference to upper gastrointestinal cancer referrals.

Results

Workload group	Total workload	Upper gastrointestinal cancer workload
Outpatients (case load)	1036	55 (5.3)
Operative (intermediate equivalents)		
Minor/intermediate	662	86 (13.0)
Major/major plus	376	4 (1.1)
Complex major	184	136 (73.9)
Total operative workload	1222	226 (18.5)

Values in parentheses are percentages

Conclusion All upper gastrointestinal cancers can be managed by one specialized surgical firm. The total number of new outpatient referrals was in line with College recommendations. However, in contrast, the total operative workload was 36 per cent greater than the recommended level, with surgery for upper gastrointestinal cancer consisting of 25 per cent of the recommended operative workload.

Five-port staging laparoscopy in oesophageal and gastric carcinoma

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Background The value of five-port staging laparoscopy in patients with oesophageal and gastric carcinoma was assessed.

Methods Five-port staging laparoscopy was performed as a short-stay procedure in 80 patients (65 men; mean age 63 (range 21–82) years) with oesophageal ($n=61$) and gastric ($n=19$) carcinoma. Five ports were used to inspect liver, omentum, peritoneal surfaces and coeliac/left gastric lymph nodes, and to obtain biopsies/cytology.

Results Satisfactory assessment was possible in 93 per cent of cases and factors precluding curative resection were demonstrated in 28 patients (35 per cent), some having more than one contraindication to surgery: hepatic metastases ($n=8$), peritoneal involvement ($n=10$), ascites ($n=8$) and lymph node spread ($n=14$). Sensitivity and specificity, respectively, for detection of spread were 100 and 98 per cent for liver metastases; 88 and 82 per cent for lymph node spread; and 90 and 98 per cent for peritoneal involvement, with 52 patients proceeding for definitive surgery and only two being irresectable.

Conclusion Five-port laparoscopy is safe, improves assessment of resectability with supplementary cannulas, and may aid

selection of patients for adjuvant therapy and make more efficient use of operating time.

Water-contrast computed tomography in the staging of gastric cancer

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Background Reports from Japan have suggested improved tumour node metastasis (TNM) staging of gastric cancer by abdominal computed tomography (CT) using water instead of low-density contrast medium as the enteral contrast. A prospective audit of patients undergoing water-contrast abdominal CT during the staging of gastric cancer was made. TNM stage by CT was compared with pathological TNM stage.

Methods Some 49 patients were recruited over 2.5 years. The diagnosis of gastric cancer was confirmed by endoscopy and biopsy in all patients; there were 46 adenocarcinomas and three lymphomas. Non-helical CT was performed with 400–600 ml tap water as enteral contrast, intravenous buscopan and contrast medium. The patient was scanned in the prone position except for patients with tumours of the cardia. All scans were reported by a single radiologist. The TNM stage by CT was compared with the pathological TNM stage of the resected specimen or with the laparotomy/laparoscopy findings in patients not undergoing resection.

Results Some 48 scans were suitable for study; patient compliance resulted in poor quality films in one patient. T status by CT was correct in 29 of 48 patients, CT tending to downstage T₃ and T₂ tumours. CT correctly identified the nine patients with linitus plastica. N status by CT was correct in 34 patients. When CT suggested node-positive disease, the accuracy was 95 per cent but this fell to 50 per cent when CT suggested node-negative disease. M status by CT was correct in 39 patients. The overall TNM stage by CT was correct in 24 of 48 patients.

Conclusion Water-contrast abdominal CT in the staging of gastric cancer provides good quality preoperative images of the tumour but accurate TNM staging is impaired by poor assessment of nodal status. Nevertheless, further staging investigation such as laparoscopy should be confined to patients with T₃ and T₄ tumours on water-contrast abdominal CT.

Anastomotic leak following oesophagectomy

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Background Anastomotic leak following oesophagectomy is a common complication and carries a mortality rate of up to 50 per cent in many series. This study reports an analysis of anastomotic leaks in a series of 79 patients undergoing oesophagectomy for carcinoma.

Methods Data were collected on 79 consecutive patients who underwent oesophagectomy for carcinoma from 1991 to 1997. Thoracoabdominal, Ivor-Lewis, transhiatal and three-stage approaches were used depending on patient co-morbidity, tumour type and level, and the preference of the two consultant surgeons undertaking the surgery. All patients had a feeding jejunostomy formed at the time of surgery.

Results There was a total of 16 anastomotic leaks (20 per cent). Eleven radiological leaks (14 per cent) were identified by routine postoperative contrast swallow at 7 days. None of these leaks created any morbidity and were treated by a nil-by-mouth regimen and continuation of enteral feeding via the jejunostomy. All of these patients had a further contrast swallow at 14 days which showed no evidence of any persistent leak in ten of the group, and they were allowed to commence oral feeding.

One patient had a persistent radiological leak which responded to gluing at 18 days. Five patients (6 per cent) experienced clinical leaks producing severe sepsis or respiratory difficulty. Two patients who had three-stage oesophagectomy underwent early exploration of the neck and insertion of large drains down to the anastomosis. Two patients with a mediastinal

leak underwent rethoracotomy, lavage and drainage. One patient with a mediastinal leak had a self-expanding metal stent placed across the anastomosis. There were no hospital deaths in these groups and all patients were eating normally at discharge.

Conclusion Successful management of oesophageal anastomotic leaks requires the presence of an established enteral feeding route and a combination of early surgical intervention, excellent intensive care facilities and close rapport with interventional radiological colleagues.

Management of oesophageal cancer in a general hospital

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Background Management of oesophageal cancer requires specialist skills. The outcome of patients with oesophageal cancer referred to one district general hospital (DGH) over a 10-year period was reviewed to see whether such skills exist in this setting.

Methods Some 128 patients were referred to one surgeon and one radiologist over the 10-year period. Sixty-six patients (51.6 per cent) underwent surgery; 60 of these had been deemed resectable before operation and this was achieved in 52 patients (87 per cent). The other six patients had planned open insertion of a Celestin tube. Sixty-two patients underwent endoscopic intubation of an irresectable tumour.

Results Some 88 patients (68.8 per cent) had adenocarcinoma, the rest having squamous cell carcinoma. In 102 patients (79.7 per cent) the tumour was in the lower third of the oesophagus; the remainder were all middle third lesions. The mean age of patients undergoing resection was 66.8 (range 42–88) years compared with 73.4 (range 30–94) years for endoscopic intubation. Forty-five of the resections were Ivor-Lewis oesophagectomies, the rest being transhiatal or three-stage procedures. The hospital mortality rate was 6 per cent for all resections (2 per cent for Ivor-Lewis). The anastomotic leak rate was 6 per cent (4 per cent for Ivor-Lewis, none fatal). For resections with 5-year follow-up data, mean survival was 36.6 months (43.2 months for Ivor-Lewis). There were three perforations (5 per cent) following endoscopic intubation and seven blocked tubes (11 per cent) requiring repeat instrumentation. Mean survival following endoscopic intubation was 3.7 months.

Conclusion These results show that oesophageal cancer can be managed in a DGH setting with acceptable outcome, if suitable expertise is available.

Anastomotic leakage can, and should, be an uncommon complication of oesophageal anastomosis following resection for cancer

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Background Leakage from an oesophageal anastomosis is a well recognized, and accepted, complication of resection for gastro-oesophageal carcinoma. Technique is important in minimizing anastomotic failure. The aim of this study was to analyse the results of all oesophageal anastomoses performed in one surgical unit over a 9-year period.

Methods Of 187 patients with oesophageal cancer, 90 underwent oesophagogastric resection (OG) with oesophagogastric anastomosis (Ivor-Lewis, 87; transhiatal (TH), three). Of 138 patients with gastric cancer, 66 underwent total abdominal gastrectomy (TAG) with oesophagojejunostomy (Roux-en-Y reconstruction). All anastomoses (except TH) were stapled.

Results Postoperative Gastrografin (Schering Health Care, Burgess Hill, UK) swallows were performed only on clinical suspicion of leakage. An oesophageal anastomotic leak was

confirmed in only two patients, one after OG (1 per cent) and one after TAG (2 per cent). Complications relating to the gastric staple line occurred in two patients after OG (fatal bleeding, one; small area of ischaemic necrosis, one). The 30-day mortality rate was 7 per cent following OG ($n=6$) and 6 per cent ($n=4$) after TAG. Six of the deaths were due to cardiorespiratory failure; only one death was attributable to anastomotic leakage. **Conclusion** Anastomotic leak rates of between 10 and 25 per cent are reported frequently after oesophageal resection. This study shows that low anastomotic failure rates can be achieved following oesophageal anastomosis. This has implications for training and accreditation of units in upper gastrointestinal surgery.

Adenocarcinomas of the lower oesophagus and cardia are similar both epidemiologically and clinically: a population-based study from 1974 to 1993

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Background Adenocarcinomas of the oesophagus and of the cardia appear to be increasing in the West. The aims of this study were to identify changes in the subsite- and subtype-specific incidences of oesophageal and gastric carcinomas in a single population of 2.5 million, and to determine whether adenocarcinomas of the oesophagus and cardia were similar in other aspects.

Methods The Merseyside and Cheshire Cancer Registry provided data on 5322 cases of primary oesophageal carcinoma and 10 573 cases of primary gastric carcinoma that were reported between 1974 and 1993.

Results Calculation of the cumulative incidence rates revealed a significant increase in oesophageal carcinoma in men over the study period; this was found to be almost entirely due to a rapid rise in adenocarcinoma of the lower oesophagus, the incidence of which trebled in men and doubled in women. The incidence of gastric carcinoma decreased between 1974 and 1993 at all subsites except the cardia, where the incidence more than doubled in men, and almost doubled in women. The similar trends in incidence of adenocarcinoma of the oesophagus and of the cardia prompted a comparison of the epidemiological and clinical parameters of adenocarcinoma occurring in the upper two-thirds of the oesophagus, lower third of the oesophagus, cardia and subcardia. Adenocarcinomas of the lower oesophagus and cardia were very similar in their changing incidence, age at diagnosis, male:female ratio, percentage of patients who smoked and in their survival. Carcinomas of both the lower oesophagus and the cardia differed significantly from those arising in the subcardia.

Conclusion This is the first population-based study to demonstrate the clinical and epidemiological similarities of adenocarcinomas of the lower oesophagus and of the cardia, which suggest that they may represent the same disease.

Loss of heterozygosity occurs on chromosome 17p and 18q in Barrett's metaplastic and dysplastic mucosa adjacent to adenocarcinoma of the oesophagus

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Background Survival from oesophageal adenocarcinoma can be improved by the earlier identification of cases suitable for surgical resection. Detection of genetic abnormalities in tissue biopsies are potential biomarkers of carcinogenesis, and the aim

of this study was to identify sites of tumour suppressor genes that are inactivated early in the Barrett's metaplasia-dysplasia-carcinoma progression.

Methods Archival, paraffin-embedded tissue from 20 oesophago-gastrectomies performed for adenocarcinoma of the oesophagus was microdissected for areas of metaplasia and varying grades of dysplasia adjacent to the adenocarcinoma. Loss of heterozygosity (LOH) analyses were performed using 11 microsatellite DNA primers used in a previous study, and known to display LOH in at least 30 per cent of fresh oesophageal adenocarcinomas. These markers were located on chromosomes 3p, 5q, 9p, 11p, 13q, 17p and 18q.

Results The detection rate of LOH in archival, paraffin-embedded tissue was lower than that detected previously in fresh tissue. However, LOH was detected in premalignant tissue on chromosomes 17p (*p53* and *TCF2* primers) in two of ten informative cases, and on chromosome 18q (*DCC* primer) in two of 12 cases. LOH at the site of the *DCC* tumour suppressor gene was detected in dysplastic and metaplastic tissue adjacent to the adenocarcinoma in both of these cases. In all cases where LOH was detected in premalignant tissue, identical LOH was also detected in the adjacent carcinoma.

Conclusion LOH at the sites of *p53* and *DCC* tumour suppressor genes can be detected in the premalignant stages of adenocarcinoma of the oesophagus, and may be useful in cancer risk assessment of patients with Barrett's oesophagus undergoing endoscopic surveillance.

Cell-surface urokinase activity in carcinoma of the oesophagogastric junction

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Background The conversion of pro-urokinase plasminogen activator (pro-uPA) to active urokinase (uPA) at a specific cell membrane receptor (uPAR) is thought to be a key step in the initiation of a proteolytic enzyme cascade enabling malignant cells to degrade the extracellular matrix during invasion. The expression of functional pro-uPA, active uPA and uPAR was investigated in patients with adenocarcinoma of the oesophagogastric junction.

Methods Samples of tumour and macroscopically normal gastric and oesophageal mucosa were obtained fresh from resected specimens ($n=19$). Antigen levels of functional pro-uPA were determined using a proteolytic activity assay. Levels of uPA and uPAR were measured in whole cell preparations by enzyme-linked immunosorbent assay.

Results

	Gastric mucosa	Oesophageal mucosa	Carcinoma	P*
pro-uPA (ng per mg protein)	0.19	0.02	0.71	0.001
uPA (ng per mg protein)	0.42	0.50	2.35	0.001
uPAR (ng per mg protein)	0.94	0.66	1.96	0.001

Values are median. *Wilcoxon matched pairs test (carcinoma versus normal mucosa)

Conclusion These data show that uPA in its precursor and active forms, together with its membrane receptor, are present at raised levels in carcinoma of the oesophagogastric junction. This is the first report of such activity in junctional carcinoma and would support the hypothesis that cell-surface activation of uPA has a role in extracellular matrix degradation in these invasive tumours.

Does tumour-associated antigen expression in cells recovered from peritoneal lavage of patients with pancreatic carcinoma predict resectability?

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Background The expression of two tumour-associated antigens which can also function as adhesion molecules (sialyl Lewis^x (sLe^x) and carcinoembryonic antigen (CEA)) was examined on cells recovered from peritoneal lavage of patients with pancreatic cancer.

Methods Sixteen patients with pancreatic carcinoma and 11 having operations for benign disease (three for chronic pancreatitis, seven for cholelithiasis and one for pancreatic cystadenoma) had peritoneal lavage with 50 ml 0.9 per cent saline at laparoscopy or laparotomy. Smear and cytospin preparations were made from the lavage fluid for conventional and immunocytochemical examination. Immunocytochemistry using antihuman CEA and antihuman sLe^x with a biotin-avidin immunoperoxidase system was used.

Results No patient had malignant cells on conventional cytological examination in either group. No patient in the benign group had cells expressing sLe^x. One patient with chronic pancreatitis had cells weakly expressing CEA. Ten of the 16 patients with pancreatic cancer had cells expressing either sLe^x or CEA (three sLe^x, six CEA, one both sLe^x and CEA). Four patients had curative resection of the tumour, the remainder being irresectable because of metastatic disease. No patient having resection expressed either sLe^x or CEA on cells recovered from the peritoneal lavage. There was a significant association with sLe^x or CEA expression and irresectability of the tumour because of metastasis ($P < 0.01$, Fisher's exact test).

Conclusion Recovery of morphologically normal cells expressing sLe^x or CEA from the peritoneal cavity of patients with pancreatic cancer is associated with advanced and irresectable disease.

Thromboprophylaxis and the incidence of deep vein thrombosis and pulmonary embolism following laparoscopic surgery

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Background Despite the increased risk of venothrombosis with laparoscopic surgery there is still great variation between surgeons' choice of thromboprophylaxis. The different thromboprophylaxis protocols have been reviewed and the venothrombotic rate following laparoscopic surgery at this hospital has been audited.

Methods A telephone survey of thromboprophylaxis regimens used by surgical firms with an established laparoscopic practice in Wales was conducted. To determine the effectiveness of these regimens an audit of venothrombotic complications at this hospital following laparoscopic procedures for the past 5 years was also conducted.

Results There were 19 surgical firms in 14 centres. Four surgical firms do not use routine prophylaxis. Of the remaining 15 firms 13 use TEDS. Seven use IPCS and 13 use miniheparin routinely. Eleven firms will alter their prophylactic regimen with high-risk patients. No firm reported venothrombotic complications that they were aware of. Between 1991 and 1996 there were 2224 laparoscopic procedures performed in this hospital. Some 1202 procedures were performed by general surgeons with the majority being laparoscopic cholecystectomy. The rest were mainly gynaecological diagnostic procedures. There were no venothrombotic complications following laparoscopic procedures during this period.

Conclusion There is great variability of choice of thromboprophylaxis between surgeons for laparoscopic surgery.

Surprisingly, the clinical result does not appear to support the increased risk of venothrombosis following laparoscopic surgery.

Endoscopic retrograde cholangiography versus percutaneous transhepatic cholangiography in the palliation of malignant obstructive jaundice: a prospective audit

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Background Endoscopic retrograde cholangiography (ERC) is considered superior to percutaneous transhepatic cholangiography (PTC) in the initial management of malignant obstructive jaundice because of its lower mortality and morbidity rates and higher success rate in relieving jaundice. The aim of this study was to test this hypothesis.

Methods Sixty-four consecutive patients who were admitted with malignant obstructive jaundice from 1 January to 30 June 1996 were audited.

Results There were 36 men and 28 women of median age 65 years. The lower third of the extrahepatic biliary tree was obstructed in 33 patients (52 per cent), the upper third in 25 patients (39 per cent) and the mid portion in six (9 per cent). The obstruction was due to carcinoma of the head of pancreas in 25 patients (39 per cent), cholangiocarcinoma in 21 (33 per cent), periampullary tumour in five (8 per cent), gallbladder carcinoma in five (8 per cent) and extrinsic compression in eight (12 per cent). Thirty-nine patients had ERC elsewhere before referral, of which only nine procedures were successful in relieving the jaundice. Sixteen of the remaining 30 patients had successful stenting in this unit by further ERC. Overall 39 patients with malignant obstructive jaundice underwent attempted ERC, but in only 22 was jaundice palliated successfully. Twenty-five of the 26 attempted PTCs were successful in relieving jaundice following stent insertion ($P = 0.0004$, Fisher's exact test). The complication rate from either procedure was minimal and was not statistically significant.

Conclusion It is concluded that PTC is an essential part of the hepatopancreatobiliary armamentarium, in relieving malignant obstructive jaundice in a tertiary referral practice.

Human thrombin receptor increases invasiveness of a human pancreatic cancer cell line

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Background The effect of human thrombin receptor (HTR) expression on invasion of the human pancreatic cancer cell line MIA PaCa-2 was assessed.

Methods The full-length HTR gene was cloned into the plasmid vector PCR3.1 in sense and antisense orientation. The HTR sense and HTR antisense clones were then transfected into the MIA PaCa-2 cell line using a lipofectin method. Expression of the HTR gene was assessed in wild-type and transfected cells using Northern blot analysis for HTR transcription. The invasion of cancer cells through an artificial basement membrane was assessed using a Matrigel invasion assay.

Results Northern blot analysis revealed a transcript of 3.8 kb for HTR with enhanced expression in sense-transfected cells. Overexpression of HTR in sense clones enhanced MIA PaCa-2 invasion when compared with wild type (mean(s.d.) 36.5(2.4), $P = 0.05$). Conversely antisense reduced MIA PaCa-2 invasion (14.9(2.3), $P = 0.08$) when compared with wild type.

Conclusion Overexpression of HTR enhances the invasion of the MIA PaCa-2 human pancreatic cancer cell line *in vitro*.

Two techniques for securing a transanastomotic stent after pancreatoduodenectomy

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Background Transanastomotic stents may reduce the incidence of pancreatic fistula, which is a leading cause of complications (sepsis, haemorrhage) and death after pancreatoduodenectomy. Two techniques to prevent premature slippage of the tube have been compared.

Methods The two techniques for securing the tube were tested consecutively among 34 patients undergoing pancreatoduodenectomy between May 1995 and May 1997. Method 1 ($n=9$) involved passage of a probe through the pancreatic duct and gland to railroad a suture through the end of the stent (4-Fr or 6-Fr infant feeding tube), which was tied on the outside of the pancreas over a polytetrafluoroethylene (GORE-TEX; W. L. Gore, Woking, UK) cuff. Method 2 ($n=18$) involved transfixing the stent with a double-ended 3/0 polydioxanone suture which was passed through the pancreas and out through the duct, and was tied over a free portion of rectus muscle. The mean length of stent within the duct was shorter in method 1 than method 2 (4.8 versus 7.8 cm, $P<0.001$). Seven patients needed no stent.

Results Two of nine patients in whom method 1 was used had minor clinical leaks from the 'blowhole' left by passage of the probe, and a third had a major leak that proved fatal despite reoperation and completion pancreatotomy. One of 18 patients in whom method 2 was used had a minor clinical leak, while another had an incidental radiological leak; the only death in this group was from a perisplenic haemorrhage. The incidence of clinical leak with method 2 was less than with method 1 ($P=0.05$). The mean daily output of pancreatic juice from the stent was 112 ml (method 1) and 80 ml (method 2). Stents remained *in situ* for 10–36 days and none fell out prematurely.

Conclusion Both techniques effectively prevent slippage of the stent, but the avoidance of passing a probe through the pancreas in method 2 diminishes the risk of postoperative fistula.

Time taken from biliary injury to the development of a symptomatic stricture

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Background Eighty per cent of benign strictures occur following injury during cholecystectomy with 75 per cent of injuries being unrecognized at the time of surgery. The aim of this study was to examine the time taken from biliary injury to the development of a symptomatic biliary stricture.

Methods The case notes of all patients presenting to this unit over the past 2 years with benign biliary stricture following cholecystectomy have been examined. Details of the initial surgery, recognition of biliary injury and its immediate management, time to the development of a symptomatic stricture and details of the stricture have been recorded.

Results Ten patients presented over the 2-year period with symptomatic biliary stricture following cholecystectomy: two presented within 6 months, four within 12 months and seven within 60 months of injury. Three patients had very delayed presentation (at 98, 228 and 276 months from cholecystectomy). In four patients the injury was noted at the time of cholecystectomy. Whether the injury was recognized and the type of repair do not appear to be related to the time to development of a symptomatic stricture. However, all those who presented with a symptomatic stricture more than 24 months from injury had stones associated with the stricture at presentation.

Conclusion Presentation of a benign biliary stricture may occur more than 5 years following injury during cholecystectomy in 30 per cent of cases. Patients presenting more than 2 years following

cholecystectomy invariably have stones associated with the stricture.

Function and nutritional changes following pancreatic and hepatic operations

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Background Pancreatic resection imposes huge metabolic demands similar to major trauma. Nutritional support may benefit these patients but evidence is lacking. The aim of this study was to measure respiratory and voluntary muscle function, psychological state and body composition following pancreatic or hepatic resection.

Methods Fifteen patients of median age 54 (range 33–80) years requiring pancreatic ($n=10$) or hepatic ($n=5$) surgery were studied. Postoperative analgesia was maintained by the Acute Pain Service. Respiratory function was assessed by spirometry and vitalography, voluntary muscle function by handheld dynamometry and psychological state was measured by Hospital Anxiety and Depression Score; fatigue was measured using a linear visual analogue scale and body fat was estimated using anthropometry and dual-energy X-ray absorptiometry (DEXA). Measurements were taken before operation and repeated on days 3 and 7 after operation.

Results

	Preoperative	Day 3	Day 7	P*
Respiratory function				
FEV ₁ (l/s)	2.4 (0.5–4.0)	1.0 (0.2–2.4)	1.4 (0.2–3.1)	<0.01
FVC (litres)	3.4 (0.8–5.0)	1.3 (0.3–3.3)	2.0 (0.3–3.7)	<0.01
PEFR (l/min)	426 (47–630)	193 (43–488)	287 (30–538)	<0.01
Muscle function				
Grip strength (N)	299 (135–499)	217 (85–383)	216 (116–407)	<0.01
Body fat and muscle				
DEXA (kg)	17.7 (5.8–53.7)	—	15.9 (6.7–53.5)	0.25
Ant (kg)	16.0 (6.1–28.1)	—	17.0 (6.8–25.1)	0.17
MAMC (mm)	234 (198–427)	229 (183–393)	227 (186–384)	<0.01
Psychology				
Anxiety	7 (0–14)	6 (1–15)	5 (0–18)	0.06
Depression	3 (1–9)	6 (3–18)	5 (1–13)	0.02
Fatigue	4.5 (0.4–8.2)	6.7 (3.7–8.9)	5.0 (1.4–8.5)	0.05

Values are median (range). FEV₁, forced expiratory volume in 1 s, FVC, forced vital capacity, PEFR, peak expiratory flow rate, MAMC, mid-arm muscle circumference. *Friedman non-parametric test

Conclusion MAMC fell significantly over 7 days suggesting a loss of muscle protein. Depression and fatigue rose following an operation implying psychological stress and fell by day 7. Both respiratory and voluntary muscle function were impaired on day 3 but only respiratory function partly recovered by day 7. This study provides evidence to support research regarding the role of nutritional support following pancreatic or hepatic surgery.

Functional, nutritional and psychological changes in severe acute pancreatitis

R. Gupta, R. Rajani, P. Jackson*, P. Taylor*, A. Jackson† and C. D. Johnson, *University of Southampton Departments of Surgery, *Medical Physics and †Nutrition, Southampton General Hospital, Southampton, UK*

Background Severe acute pancreatitis is associated with local and systemic complications which may affect respiratory and muscle function, psychological state and body composition.

These variables have been measured to define their natural history in patients with severe acute pancreatitis treated with aggressive nutritional support.

Methods Twelve patients (six men) of median age 61 (range 38–89) years with severe acute pancreatitis as determined by an Acute Physiology And Chronic Health Evaluation II score of 6 or more were studied. Respiratory function was assessed by spirometry and vitalography, voluntary muscle function by handheld dynamometry, psychological state by the Hospital Anxiety and Depression Score, fatigue using a linear visual analogue scale, and body fat by anthropometry and dual-energy X-ray absorptiometry (DEXA) within 24 h of admission, and on days 3 and 7. All patients received aggressive parenteral or enteral nutritional support

Results

Variable	Day 0	Day 3	Day 7
FEV ₁ (l/s)†	1.2 (0.4–3.0)	1.6 (0.3–2.9)	2.3 (0.5–3.9)
FVC (litres)†	1.5 (0.5–3.7)	2.0 (0.5–3.8)	2.9 (0.8–5.1)
PEFR (l/min)*	304 (73–535)	382 (57–557)	439 (93–690)
Grip (N)	201 (127–526)	205 (92–461)	213 (113–477)
Fat (DEXA) (kg)	28.2 (14.2–55.2)	—	29.3 (15.4–61.1)
Anxiety	10 (4–17)	8 (0–20)	6 (0–17)
Depression*	6 (1–16)	9 (1–17)	5 (1–13)
Fatigue (cm)†	7.8 (3.9–9.6)	6.1 (0.3–9.1)	3.1 (0.4–8.1)

Values are median (range). FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. PEFR, peak expiratory flow rate. * $P < 0.05$, † $P < 0.01$ (Friedman non-parametric test)

Conclusion This study demonstrates an improvement in respiratory function, depression and fatigue in patients with severe acute pancreatitis treated with aggressive nutritional support. Further research is warranted to investigate the mechanism of this improvement and the impact of other therapeutic agents in these patients.

Laparoscopic mesh repair with epigastric port-site gastropexy for paraoesophageal hernia

G. Smith and T. C. B. Dehn, *Royal Berkshire Hospital, Reading, UK*

Background Laparoscopic mesh repair with epigastric port-site gastropexy was evaluated in the treatment of symptomatic paraoesophageal hernia. This condition occurs predominantly in the elderly, and complications and urgent repair have a high associated mortality rate.

Methods Sixteen patients were followed prospectively. Laparoscopic reduction of hernia, mesh repair of hiatus and epigastric port-site gastropexy was performed in 14 patients.

Results At mean follow-up of 18 (range 1–42) months 13 patients were symptom free. Median postoperative stay was two nights. There were no deaths and one recurrence.

Conclusion It is concluded that this technique for the treatment of paraoesophageal hernia provides a satisfactory alternative to open repair.

Gastric carcinoma. A curable disease in Wales?

M. Chatterton, R. England, R. Kerwat, E. D. Srivastava, M. C. Allison and W. G. Lewis, *Department of Surgery, Royal Gwent Hospital, Newport, UK*

Background A recent report from Leeds suggested that considerable delays still occur in the diagnosis of gastric cancer.

The mortality ratio for gastric cancer in Wales, at 33.5 deaths per 100 000, is significantly higher than that of the rest of the UK, at 23.4. The time taken to diagnose gastric cancer in a large district general hospital in South Wales was quantified and the source of any delay identified.

Methods Sixty consecutive patients (median age 69 (range 35–86) years; 40 men, 20 women) with gastric cancer were assessed prospectively. Stage of disease at presentation was I, II, III and IV in six, nine, 31 and 14 patients respectively.

Results

Period of delay	Time (weeks)	Percentage of total delay
Symptoms to seeing a doctor	12 (1–104)	49
Seeing doctor to hospital referral	1 (1–128)	19
Referral to consultation/open access endoscopy	1 (1–31)	7
Hospital consultation to diagnosis	2 (1–87)	16
Diagnosis to treatment	2 (1–23)	18
Total delay to diagnosis	23 (1–175)	—
Total delay to treatment	28 (2–185)	—

Values are median (range)

Conclusion Significant delays still occur in the diagnosis of gastric cancer. In this series, 68 per cent of the total delay occurred in the community and no fewer than 75 per cent of the tumours were advanced stage III and IV. To achieve diagnosis of gastric cancer at an earlier and potentially curative stage, measures are required to reduce delays in the community.

Use of immediate postoperative tunnelled jejunal feeding and subsequent nutritional status in patients undergoing oesophagogastrectomy

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Background The success of postoperative jejunal feeding was evaluated in patients undergoing oesophagogastrectomy and their subsequent nutritional status was monitored.

Methods Fresenius tunnelled jejunal feeding tubes were inserted at surgery. Nutritional requirements were calculated; feeding commenced after operation until restoration of adequate oral intake. Nutritional requirements were calculated 1 month after operation and compared with intake from 24-h dietary recall. Weight and anthropometric measurements (triceps skinfold thickness (TST) and mid-arm muscle circumference (MAMC)) were reported before operation, on discharge, at 1 month after operation and periodically thereafter.

Results Twenty patients (15 men) underwent oesophagogastrectomy. Jejunostomy feeding commenced within 48 h in 18 and continued for 9 (range 3–20) days. Major tube complications occurred in one patient and minor complications in one patient. There were no deaths. Major morbidity occurred in four patients. Two patients have died from metastases and two have recurrence. Following oesophagogastrectomy, median weight change was 0 (range –9.4 to +5.5) kg on discharge and –1.6 (range –7.3 to +5.9) kg between discharge and 1 month. Nutritional requirements were met by 47 per cent of patients at 1 month. Of 15 patients followed for up to 4 months 77 per cent had maintained (± 2 kg) or gained weight. Median weight changes were +0.9 (range –3.1 to +3.6) kg. Subsequent measurements indicated weight maintenance in about 90 per cent of patients without recurring disease. Anthropometry in 15 of 20 patients showed reduction in MAMC and TST at 1 month

of 80 and 54 per cent respectively; of ten patients who subsequently had anthropomorphic measurements, four and nine showed maintenance or improvement in MAMC and TST respectively.

Conclusion Tunnelled jejunostomy feeding is effective after oesophagogastric resection. The ability to meet nutritional requirements reflects recorded weight changes.

Laparoscopic fundoplication: early lessons from the first 100 cases

G. Smith and T. C. B. Dehn, *Royal Berkshire Hospital, Reading, UK*

Background Unplanned returns to theatre in patients who had undergone laparoscopic Nissen fundoplication (LNF) for gastro-oesophageal reflux disease were reviewed.

Methods From a comprehensive prospective database details of unplanned returns to theatre were examined.

Results From January 1993 to May 1997, 100 LNFs were performed at this hospital and there were nine unscheduled returns to theatre, seven of these in the first 35 patients. Causes were wrap herniation (four patients), dysphagia (three), bleeding (one) and oesophageal carcinoma *in situ* (one).

Conclusion Changes in operative technique have been made. The crura are now closed routinely, a greater degree of fundal motility is obtained and there have been changes in technique for obtaining haemostasis.

Assessment of the role of endoluminal ultrasonography in staging of upper gastrointestinal malignancy

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Background Preoperative staging is of value in planning rational treatment approaches in upper gastrointestinal malignancy, but imaging techniques currently used may inaccurately stage tumours. Endoluminal ultrasonography (EUS) has been suggested to improve the accuracy of preoperative staging. Initial experience of this imaging technique since its introduction in this unit has been audited.

Methods Between May 1996 and May 1997, 41 patients (14 female, 27 male; 26 with gastric carcinoma, 15 with oesophageal carcinoma) underwent preoperative staging with EUS in addition to abdominal and thoracic computed tomography, before attempted surgical resection. Surgical treatment included 30 potentially curative resections with radical lymphadenectomy, eight palliative resections, two staging laparoscopies with biopsy, and one open and close laparotomy. Five patients had disease unassessable by EUS (three non-traversable oesophageal lesions; one gastric tumour not identified at EUS; one gastric outlet obstruction with large amounts of food residue in the stomach precluding adequate assessment). Thirty-six patients had assessable tumours and were staged according to the 1987 tumour node metastasis (TNM) classification for gastric and oesophageal carcinoma. Operative and histological staging was carried out on all patients and each element of the TNM staging was compared to assess the accuracy of the EUS stage.

Results Comparing histological T stage with that of EUS, in 17 of 36 patients the two were in agreement. Nine patients were understaged and nine overstaged by EUS (each by one T stage). Comparing the N stage assigned on histological assessment and on EUS, in 23 of 36 the two were in agreement. EUS overstaged three patients by one N category and understaged ten patients (seven patients by one N category, three patients by two N

categories). In two patients metastatic liver disease was identified at EUS which had not been demonstrated by abdominal spiral computed tomography.

Conclusion The accuracy of EUS has not been as high as initially hoped in assessment of upper gastrointestinal malignancy. Despite this, useful complementary staging information has been obtained and EUS complements spiral computed tomography. As experience increases, the accuracy of this technique may improve.

Palliation of gastric carcinoma with radiologically placed expandable metallic stents

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Background Stenting of malignant oesophageal tumours with expandable metallic stents under radiological control is an established method of palliation of such tumours. The aim of this study was to assess the feasibility of palliating obstructing malignant gastric tumours in a similar fashion.

Methods Six patients have been treated with gastric stents. All were men, with age at presentation ranging from 58 to 84 years. The diagnosis of gastric carcinoma and assessment of resectability were made using a combination of barium swallow, endoscopic biopsy and computed tomography. Meditech or Schneider uncovered expandable metallic wallstents 10 or 15 cm long, with a diameter when expanded of 18 or 22 mm, were placed under fluoroscopic guidance either as a primary procedure or following failure of another attempt at palliation. A barium swallow was performed to assess the degree of success of placement and expansion of the stent.

Results All tumours extended from the oesophagogastric junction distally for between 5 and 10 cm. One also extended into the distal oesophagus. Four patients had an expandable metallic stent placed as the primary procedure. One patient, with a potentially resectable tumour, was found to be inoperable at laparotomy and placement of a Celestin tube failed. One patient had an endoscopically placed non-expandable rubber-covered stent which failed. On subsequent barium swallow, four stents were satisfactorily placed and expanded, with free passage of contrast. One stent was in the correct position but required dilatation under fluoroscopic and then endoscopic control. One was placed too distally and a second stent was successfully positioned above and overlapping the first. All patients were able to take a semisolid diet following deployment of the stent. Follow-up currently ranges from 1 week to 8 months and to date no patient has required further palliation of dysphagia.

Conclusion Radiologically placed expandable metallic stents can be used to palliate dysphagia in patients with gastric carcinoma and are a valuable addition to the management options in this condition.

Scanning laser Doppler flowmetry and continuously recirculating intraluminal gas tonometry in the assessment of gastric perfusion during oesophagectomy: an initial report

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Background Of the aetiological factors associated with leak and benign stricturing of the anastomosis following oesophageal resection and reconstitution of gastrointestinal continuity with a gastric tube, ischaemia caused by poor perfusion at the gastric end of the anastomosis is thought to be most important. This study aimed to assess the new techniques of intraoperative

scanning laser Doppler flowmetry and continuously recirculating gas tonometry, and their ability to detect changes in gastric perfusion during oesophagectomy.

Methods Five patients undergoing oesophageal resection for malignancy were studied. After initial assessment that the tumour was resectable, tonometer balloons were placed in the stomach and proximal jejunostomy (alongside a feeding jejunostomy catheter). Measurement of blood pressure, central venous pressure, arterial pulse rate and blood gases as well as gastric and jejunal intramucosal pH (pH_i) and a laser Doppler scan of the stomach were made at three time points: before gastric mobilization, after division of left gastric and left gastro-epiploic vessels and, finally, after formation of the anastomosis. In each subject, from a grey-scale photographic image of the stomach and anastomosis produced by the scanning laser, identical regions of interest (ROIs) each of 1.5 cm² were interrogated from each scan, these representing the area of anastomosis, the gastric corpus and the antrum. Mean perfusion units (PU) from the 1750 individual measurements taken within the ROI were then calculated for each of these areas.

Results There were no significant changes in cardiovascular measurements between each time point but there were significant falls in perfusion measured with the scanning laser Doppler in all subjects and in all areas of the stomach. Mean perfusion of the stomach was 78.6 PU before mobilization and this fell to 42.4 PU after mobilization representing a mean fall of 46 per cent. There was a gradient of reduced perfusion between the antrum (fall 33 per cent, $P < 0.05$) and the area used for the anastomosis in the fundus (mean fall 52 per cent, $P < 0.001$). After formation of the anastomosis, mean perfusion at the gastric end of the anastomosis was 42.4 PU (mean fall 51 per cent, $P < 0.0005$). Before mobilization mean gastric and jejunal pH_i were 7.39 and 7.45 respectively. These values changed to 7.10 and 7.34 respectively after mobilization, and to 7.24 and 7.33 after anastomosis formation.

Conclusion This pilot study confirms that both these techniques can be used at operation to assess changes in gastric perfusion during oesophagectomy. Furthermore significant falls in perfusion in that part of the stomach used for the gastro-oesophageal anastomosis were observed between the start and end of surgery. Further study is needed to assess whether these methods

can be used to predict ischaemia-related anastomotic complications.

p53 immunoreactivity and free peritoneal cells: poor prognostic markers in gastric cancer

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Background The aim of this study was to demonstrate the relationship between expression of p53 protein, peritoneal malignant cytology and prognostic significance for patients with gastric cancer.

Methods Patients undergoing laparotomy for histologically proven gastric cancer were recruited over a 2-year period. At laparotomy peritoneal cells were sampled by a combination of techniques including washings, brushings and imprint cytology. Peritoneal cellular specimens were assessed for morphological features of malignancy using Papanicolaou and Giemsa stain. Sections of the resected specimen were examined with a monoclonal antibody to p53. Slides were interpreted by two independent observers. Patients were followed for at least 2 years or until death. Survival differences were compared by the log rank test.

Results Some 87 patients were recruited. p53 immunoreactivity was detected in 17 patients; 18 patients had malignant cytology. There was no significant association between samples containing malignant cells and p53-positive histology ($\chi^2 = 2.74$, 1 d.f., $P = 0.1$). Eleven patients had positive p53 staining but showed no morphological features of malignancy in peritoneal cytology. Twelve had morphologically malignant cytology but negative p53 expression. p53 staining was associated with a poor prognosis ($\chi^2 = 5.63$, 1 d.f., $P = 0.018$) but the association of survival with morphologically diagnosed malignant cytology was stronger ($\chi^2 = 25.1$, 1 d.f., $P < 0.0001$).

Conclusion p53 expression in gastric cancer correlates poorly with standard morphological diagnosis of malignant cytology. While there is an association between detection of p53 expression and survival, the association remains stronger for detection of malignant cytology by standard techniques.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Bacterial translocation in multiple organ failure: cause or epiphenomenon still unproven

Sir

In a previous publication I presented data on endotoxin assays in patients who were developing acute renal failure, the rise of lipid A antibody titres in patients admitted to the intensive care unit, and discussed experiments on absorption of endotoxin through the jejunal mucosa of rats¹. Endotoxin labelled with 51-chromium is not absorbed through freshly created jejunal sacs, but it is when the mucosa has been washed with ethylenediamine tetra-acetic acid to remove mucoproteins. The relevance of this to multiple organ failure is that a period of gut mucosal ischaemia of only 30–45 min is sufficient to stop the epithelial synthesis of protective glycoproteins before endotoxin can be absorbed.

Readers should consider the article by Lemaire *et al.* (*Br J Surg* 1997; 84: 1340–50) knowing that it is not necessary to have gut epithelial damage, but merely cessation of glycoprotein synthesis, to get absorption of endotoxins from the gut lumen and bacterial translocation. I would insert endotoxin absorption through the epithelium in Fig. 1.

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1 Wardle EN. Acute renal failure and multiorgan failure. *Nephrol Dial Transplantation* 1994; 9 (Suppl 4): 104–7.

Long-term oral administration of branched chain amino acids after curative resection of hepatocellular carcinoma: a prospective randomized trial

Sir

I read with interest the paper by the San-In group of liver surgery (*Br J Surg* 1997; 84: 1525–31) who conclude that long-term nutritional support with branched chain amino acids (BCAAs) after resection of hepatocellular carcinoma is beneficial in improving clinical features and laboratory data after hepatic resection. Can this claim be substantiated from the data provided?

First, crucial data on nutritional intake of both groups of patients was not provided. The patients receiving the BCAA supplement took 100 g per day of Aminoleban EN (27 g of protein) (Otsuka, Tokyo, Japan). What was the total nitrogen and calorie intake of these patients and the control group during this time? It is not sufficient to say that 'patients ate their usual meals' as dietary recalls are notoriously unreliable. Did the control group have an adequate nitrogen and calorie intake and was it equal to or less than that in the BCAA group? If less, it is possible that any beneficial effect has nothing to do with BCAAs and may simply be the effect of an increased nutritional intake in the BCAA group. The study did not control for ingestion of other minerals and vitamins (increased in BCAA group). Could any beneficial effects have been mediated by these additional nutrients, many of which can modulate key immune and metabolic processes?

Second, multiple analyses of several variables and at multiple time points were performed. By chance, one in 20 tests can give a significant result (a type 1 error) and, therefore, correction factors should have been used to reduce this risk. The number of subgroup analyses that were carried out on the different Child

categories raises concerns which are well documented, unless these were planned in advance in the protocol¹.

Third, the benefits of BCAAs occurred in the first 3 months of the study and if patients' performance status was 70 or less, and not over the whole period. Is it correct to assume that there were also no benefits during a mean follow-up of 36 months? There is evidence to show that certain types of human tumours can be stimulated *in vivo* by the exogenous administration of nutrients. In patients with colorectal cancer the stimulatory effects of both a standard nutritional regimen and a BCAA-enriched parenteral nutrition on tumour protein synthesis, a primary determinant of tumour growth, have been reported previously^{2,3}.

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- 1 Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1993: 466–7.
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- 3 McNurlan MA, Heys SD, Park KGM, Broom J, Brown DS, Eremin O *et al.* Tumour and host tissue responses to branched-chain amino acid supplementation of patients with cancer. *Clin Sci (Colch)* 1994; 86: 339–45.

Author's reply

Sir

Although many studies have reported the short-term effect of parenteral and enteral supplementation of branched chain amino acids (BCAAs) on hepatic encephalopathy, protein synthesis and overall nutrition in acute and chronic liver disease, there are few studies of long-term effects. The previous workers have already given precise data of the nitrogen balance and other nutritional parameters by BCAA supplementation. Our study was carried out to investigate whether long-term oral supplementation of BCAA was beneficial in patients with curative hepatic resection for hepatocellular carcinoma (HCC). The evaluation of patients was therefore performed at outpatient clinics and we did not measure the total nitrogen and calorie intake in either group of patients. Although it is assumed that the significant increase in Fischer's molar ratio was due to ingestion of Aminoleban, was the significant increase in body-weight due solely to the treatment that supplied only 27 g of protein per day? We suggest that the increased BCAA and decreased aromatic amino acid levels in blood may have modified the entry of tryptophan into the brain with the synthesis of serotonin, thus inducing increased appetite in the patients treated with BCAA¹.

We agree with the second comment on the type 1 error and the problem of retrospective stratification. As indicated, there were significant differences at only several time-points for some data but we do not think that such differences are meaningless. The differences in performance status, body-weight and Fischer's ratio were continuously significant during the observation, which could be assumed as a significant overall effect of the treatment, although the underlying mechanism remains to be elucidated.

Third, it is true that statistical differences decreased for various parameters 3–6 months after treatment. The differences in performance status, body-weight and Fischer's molar ratio were observed for 12 months of treatment. Our anticipation was

enhanced growth of possible residual HCC cells or enhancement of metachronous carcinogenesis in the remnant liver. It is likely that this did not occur in our study. At present, little is known about the effect of BCAA supplementation on the growth of human HCC. Our subsequent *in vitro* study shows that high concentrations of BCAA suppress the growth of human HCC cells. These data will be reported elsewhere.

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- 1 Krause R, James JH, Ziparo V, Fischer JE. Brain tryptophan and the neoplastic anorexia-cachexia syndrome. *Cancer* 1979; 44: 1003-8.
- 2 Cangiano C, Laviano A, Meguid MM, Mulieri M, Conversano L, Preziosa I *et al.* Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *J Natl Cancer Inst* 1996; 88: 550-2.

Statistical commentary

Sir

This correspondence raises a number of interesting issues. Looking back at the original article, I am relatively happy that the authors have demonstrated that long-term support with branched chain amino acids (BCAAs) led to an increase in weight which was sustained over 12 months and which was not associated with any gross effect on survival or tumour recurrence. Had the authors reported confidence intervals it would have been easier to assess how much weight to place on these negative findings for survival and recurrence.

In the context of a pragmatic clinical trial I also agree with the authors' implied comment that the precise mechanism of the increase in weight is not particularly important.

Where I agree strongly with Mr Heyes is that the authors have looked too closely behind their overall (encouraging) findings. The paper reports the results of over 200 statistical tests, which makes the fine detail all but uninterpretable. In Fig. 2, for example, is it really plausible that BCAAs should affect the red blood cell count only in patients with Child grade A disease, and the platelet count only in those with Child grades B and C disease?

The multiple comparisons have been generated via multiple outcome measures, multiple time-points and multiple subgroups. There are appropriate statistical strategies for handling all of these issues¹, but the guiding principle should always be 'Keep it Simple'.

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Statistical Advisor
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- 1 Murray GD. Statistical aspects of research methodology. *Br J Surg* 1991; 78: 777-81.

Hand-held Doppler as a screening test in primary varicose veins

Letter 1

Sir

We read with interest the recent paper by Campbell *et al.* (*Br J Surg* 1977; 84: 1541-3) and would like to comment.

The authors found that of the nine patients in whom hand-held Doppler failed to detect reflux, six had a competent saphenofemoral junction in the presence of long saphenous vein (LSV) reflux on duplex scanning. We have observed this phenomenon in both the long and short saphenous systems¹. This

has important implications: clearly ligation of either the saphenofemoral junction or saphenopopliteal junction alone in these patients is inappropriate as it would fail to control or remove the incompetent segment of vein. Clinically significant varices may arise from long saphenous veins where the saphenofemoral junction is competent and we would suggest that this could be detected by insonation of the LSV at the mid-thigh or knee level with a hand-held Doppler. The authors may therefore have missed detectable long saphenous reflux.

The authors have confirmed previously reported observations that hand-held Doppler is unreliable in the assessment of veins in the popliteal fossa. The anatomical complexity of veins in this region is probably the main reason for diagnostic difficulty. This paper shows that hand-held Doppler detects a substantial number of incompetent veins in the popliteal fossa but misses some with popliteal vein and short saphenous vein incompetence. This is not a major limitation in patients presenting with primary varicose veins, the group selected by the authors for this study, but is an important point to remember when investigating patients with more severe venous disease. Any patient in whom this test demonstrates venous incompetence in this region should therefore be referred for duplex ultrasonography, since the exact location of incompetent veins in this region does make a difference to patient management. We would not embark on surgery for saphenopopliteal junction reflux without conducting preoperative ultrasonography marking to aid in identifying the anatomy of the popliteal fossa.

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- 1 Abu-Own A, Scurr JH, Coleridge Smith PD. Saphenous vein reflux without incompetence at the saphenofemoral junction. *Br J Surg* 1994; 81: 1452-4.

Letter 2

Sir

The paper by Campbell *et al.* was timely and helpful. The Doppler method employed by the authors for detecting long saphenous vein (LSV) incompetence was to insonate the groin while squeezing and releasing the calf, and a similar examination while insonating 10 cm below the groin. I find it helpful to insonate at the groin while compressing the varices and, if reflux is not detected, then to insonate over the LSV just above the knee while compressing and releasing the varices. Compressing and releasing the varices rather than the calf tends to generate louder velocity signals, and insonating the LSV just above the knee will detect reflux in the vein associated with an incompetent communication with a deep system other than the saphenofemoral junction, for example an incompetent mid-thigh perforator.

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Author's reply

Sir

It is interesting that the individual experiences of venous enthusiasts using hand-held Doppler are so similar. Like Messrs

Abu-Own and Coleridge Smith we now often insonate the long saphenous vein (LSV) in the lower thigh or at knee level, especially when there is no reflux in the groin. At the time of our study we used the Trendelenburg test to detect reflux both at the saphenofemoral junction and lower down the LSV. We considered it important to evaluate this traditional test but have now abandoned its routine use as mentioned in our discussion.

We strongly agree that the LSV should be stripped to eliminate reflux distal to the groin. Routine stripping of the short saphenous vein is more controversial because many surgeons believe that it poses a high risk of sural nerve damage. However, we strip this vein to the ankle when duplex scanning has shown it to be large or when it is easily palpable.

We thoroughly endorse the practice of referring any patient with reflux in the popliteal fossa for duplex scanning. The report should specify the exact location of the saphenopopliteal junction, so that it can then be marked with greater confidence using hand-held Doppler just before operation; this saves a second duplex scan.

With regard to Mr Pardy's comments, his technique of compressing the varicose veins during hand-held Doppler examination is a good compromise between two of the methods we used: squeezing the calf and tapping on the veins. We used calf squeezing because it is the same stimulus as that used during duplex examination, aimed at achieving substantial movement of blood up the veins of the limb. It is also applicable when there are few or no varicose veins to see.

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Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units

Letter 1

Sir

This work (*Br J Surg* 1997; 84: 1370–6) may become an important reference for the future but a little caution must be exercised in accepting these results at face value.

The results were obtained by pro forma questionnaire and the reoperation and in-hospital death rates obtained by the same means. It is not clear whether the data were prospective, retrospective or whether the patients were consecutive. It is not clear whether the in-hospital deaths were related to surgery, or within or without the conventional 30-day limit. There were no data on out-of-hospital deaths that may or may not have been related to the surgery. There was no validation of the data by external auditors or independent observers.

The power of such a study is less than that of equally large studies (such as European Carotid Surgery Trial¹ and North American Symptomatic Surgery Trial²) in which the numbers and outcomes were reported not by the participating surgeons but by neurologists.

The value and cost–benefit issue was not addressed and it is not possible to draw conclusions from this as to whether or not pancreatotomy should be undertaken in a cash-strapped national health service.

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1 European Carotid Surgery Trial. Interim results for symptomatic patients with severe (70–90 per cent) or with mild (0–29 per cent) carotid stenosis. *Lancet* 1991; 337: 1235.

2 North American Symptomatic Surgery Trial. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. *N Engl J Med* 1991; 325: 445.

Letter 2

Sir

This paper presents data on 1026 resections for pancreatic and periampullary tumours from 'selected centres'. From these data and some complex data analysis the authors draw the conclusions that results from 'specialist units' in the UK are superior to those in non-specialist units and that mortality rates are generally lower in units with a higher case-load. These conclusions run contrary to the University Hospitals Consortium and Department of Veterans Affairs studies quoted in the paper. Deficiencies in the paper need to be considered before the authors' conclusions are accepted. First, basic information on morbidity including pancreatic anastomotic leak rates is not provided. Second, annual resection rates per institution range from 0.3 to 16 with only six institutions performing more than ten resections per year. Thirteen institutions perform six or fewer resections per year, and these units provided 399 of the 1026 patients reported in this study. Third, six university hospitals had more than one surgeon performing resections which included a professor with a major interest in vascular surgery and a surgeon with a major interest in breast disease. The results of specialist pancreatic surgeons, not institutions, should be analysed and data provided on the number of patients per surgeon.

General surgery has subspecialized greatly and in many district general hospitals all major upper gastrointestinal (GI) resections are performed by an upper GI surgeon¹. The Royal College of Surgeons seeks to encourage the development of acute general hospitals serving a population of 450 000 to 500 000². The population base suggested by the authors of this paper for a specialist pancreatic unit is between 600 000 and 850 000. Such a population is too large for the acute general hospital and too small for a regionally based service. Are the authors recommending specialization of pancreatic surgery to upper GI surgeons within the acute general hospital?

Morbidity and mortality data for pancreatic surgery collected from district general hospitals with well established upper GI subspecialists may help to clarify the appropriate arrangements for pancreatic surgery in the UK.

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- 1 Eyre-Brook IA, Dix F, Gee AS. What is an upper GI surgeon? *Br J Surg* 1998; 85: 414.
- 2 Consultant surgical practice and training in the UK. The senate of surgery of Great Britain and Ireland.

Letter 3

Sir

We read with interest the paper by Neoptolemos *et al.* (*Br J Surg* 1997; 84: 1370–6) describing the relationship between hospital mortality and case-load for the resection of pancreatic and periampullary tumours in the UK. These results are in agreement with large reports from the USA^{1,2}. The authors also report a low mortality rate of 6 per cent. We have a few points we would like to address.

As the study comprises a survey, it is of interest to know the criteria by which a unit was selected for the study and what the response rate of the survey was. As information on 35 institutions was excluded, would this have affected the overall mortality in the study? It has been demonstrated recently in two studies^{3,4} concerning bile duct injury that surveys show more

advantageous results than audit studies. The study by Neoptolemos *et al.* included patients undergoing enucleation, local resection and left resection (12 per cent 'smaller' operations) and this may have influenced the outcome of the study favourably. Could the authors provide the mortality rate of Whipple procedures separately?

How did units select a particular study period for inclusion of patient material, and what was the reason to accept such a wide variability of time-periods? It has been shown that there is a relationship between mortality and year of operation¹.

Table 1 In-hospital mortality in 1994 and 1995 in the Netherlands (four categories according to hospital volume)

Hospital volume	No. of patients	Discharge home	Discharge to other hospital	No. of deaths
<5	195	151	13	31 (15.9)
5-9	87	79	0	8 (9)
10-24	80	68	5	7 (9)
≥25	66	63	2	1 (2)*
Total	428	361	20	47 (11.0)

Values in parentheses are percentages. * $P < 0.05$ compared with small-volume hospital (fewer than five resections per year)

We recently performed a study in which all pancreatoduodenectomies performed in 1994 and 1995 from the Netherlands were included⁵ and demonstrated a correlation between mortality and case-load. There was an increased hospital mortality rate in low-volume centres (Table 1). Unbiased results from all centres throughout the UK will probably show a similar mortality and this might be another argument for centralization of this type of surgery.

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- 1 Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. *Ann Surg* 1995; 221: 43-9.
- 2 Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy *Ann Surg* 1995; 222: 638-45.
- 3 Nair RG, Dunn DC, Fowler S, McCloy RF. Progress with cholecystectomy: improving results in England and Wales. *Br J Surg* 1997; 84: 1396-8.
- 4 Richardson MC, Bell G, Fullarton GM and the West of Scotland Laparoscopic Cholecystectomy Audit Group. Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit in 5913 cases. *Br J Surg* 1996; 83: 1356-60.
- 5 Gouma DJ, de Wit LT, van Berge Henegouwen MI, van Gulik TM, Obertop H. De relatie van ziekenhuiservaring en ziekenhuisterfte na partiële pancreatoduodenectomie in Nederland. *Ned Tijdschr Geneeskde* 1997; 141: 1738-41.

Letter 4

Sir

We were interested to read of the low mortality rate following pancreatic resection in 1026 patients but are unclear as to the definition of a 'specialist unit' and the criteria for inclusion.

We work in large adjacent district general hospitals serving populations of 250 000 (N.D.K.) and 380 000 (I.M.P.) and have been in post 2.5 and 5 years respectively. We have an interest in

hepatopancreatobiliary surgery and have an experience of 36 resections of the pancreatic head, of which 11 were pylorus-preserving. Five patients underwent vascular reconstruction at surgery with isolated portal vein reconstruction in four for tumour involvement. The fifth underwent a successful reconstruction of the superior mesenteric artery using the splenic artery combined with portal vein reconstruction for a low-grade sarcoma arising in the pancreatic head and encasing both vessels. One patient died during isolated portal vein reconstruction, one of two patients where a vascular surgeon was also involved in the reconstruction. The operative mortality rate of 3 per cent compares favourably with that of 4.9 per cent in the article. We believe that results are related to volume and our case-load of four to five resections per year is similar to the figure of 5.5 resections in 'specialist units'.

We agree that the mean resection rate for pancreatic cancer is low and believe it is because gastroenterologists do not refer patients appropriately, perhaps because of a perception that pancreaticoduodenectomy is accompanied by unacceptable morbidity and mortality.

We believe that hepatopancreatobiliary surgery should be offered by surgeons with a demonstrable interest in this specialty but do not accept that patients need to be sent to specialist units for surgery.

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Authors' reply

Sir

In response to the letter from Mr Adiseshuah, the data analysed in this study were of consecutive patients collected over defined periods (see paper). Contributors were not asked to specify whether data were collected prospectively or not. The mortality figures presented were of all in-hospital deaths. Information about specific postoperative complications was requested but was incompletely returned and therefore was not analysed.

Mr Eyre-Brook raises the question of the results from individual surgeons rather than institutions. Sufficiently powered studies are required to allow a response. This and other studies, including the data reported in the letter from the Netherlands, have shown a statistically significant inverse correlation between institutional case-load and postoperative mortality¹⁻³. This relationship does not hold for individual surgeons. Presumably this is because the diagnosis, preoperative assessment, anaesthetic support and postoperative care requires a sophisticated multidisciplinary approach which supercedes the contribution of any individual surgeon. The data also show that the minimum population base for a specialist pancreatic unit should be between 600 000 and 850 000 and therefore needs to be at regional or subregional level.

The surgeons from Guildford are congratulated on their initial experience with good results performing four to five pancreatic resections per year. The data from this and other studies, however, show very clearly that at least five to seven resections for pancreatic ductal adenocarcinoma (or at least ten resections for pancreatic and periampullary tumours combined) per institution per year are required to achieve an acceptable postoperative mortality rate of about 6 per cent or less.

The principle conclusion of this study was that case-load was highly statistically inversely related to postoperative in-hospital mortality. If done by specialists the postoperative mortality rate

is less than 6 per cent; if done by generalists it is about 30 per cent⁴. It is possible that long-term survival is improved by specialist treatment; this has been shown to be the case in breast carcinoma⁵, for example, but there are no data for pancreatic carcinoma.

It is disappointing that none of the UK correspondents are participating in multicentre trials of adjuvant treatment (such as ESPAC-1⁶) and we would encourage them to enrol future patients in such studies.

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- 1 Glasgow RE, Mulvihill SJ. Hospital volume influences outcome in patients undergoing pancreatic resection for cancer. *West J Med* 1996; 165: 294–300.
- 2 Gordon TA, Burleyson MHS, Tielsch JM, Cameron JL. The effects of regionalisation on cost and outcome for one general high-risk surgical procedure. *Ann Surg* 1995; 221: 43–9.
- 3 Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 1995; 222: 638–45.
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- 5 Gillis CR, Hole DJ. Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland. *BMJ* 1996; 312: 145–8.
- 6 Neoptolemos JP, Baker P, Beger H *et al.* A randomized multicentre European study comparing adjuvant radiotherapy, 6-mo chemotherapy and combination therapy vs no-adjuvant treatment in resectable pancreatic cancer (ESPAC-1). *Int J Pancreatol* 1997; 21: 97–104.

Book reviews

Organ and Tissue Donation for Transplantation

J. R. Chapman, M. Deirehoi and C. Wight (eds). 250 × 178 mm. Pp. 474. Illustrated. 1997. London: Arnold. £75.

This book addresses the worldwide problem of the critical shortage of organs for transplantation. It is divided into three main sections addressing attitudes to organ donation in society, the process of organ donation, and methods of increasing organ donation. The contributions are very broad ranging and will appeal not only to transplant coordinators, surgeons and physicians, but also to patients and other members of the public who have an interest in this difficult area. The text contains a number of detailed analyses of data relating to the organ shortage problem; these are well presented and up to date and this book will be especially helpful to anyone involved in the important process of disseminating the organ shortage message. My only criticism is that very little attention has been given to non-heart-beating organ donation which is such a controversial and topical subject that a specially dedicated chapter would not be out of place. Organ and tissue donation for transplantation makes an original contribution to the transplant literature and I would envisage that it will become a useful reference source for members of the transplant community.

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Year Book of Vascular Surgery – 1997

J. M. Porter (ed.). 235 × 160 mm. Pp. 534. Illustrated. 1997. St Louis, Missouri: Mosby £57.

John Porter's commentaries enliven an abstract collection of papers that vascular surgeons will have read, heard of from literate or ambitious registrars, or missed entirely. Some comments are amusing: 'clearly when treating a rat for colonic segmental ischaemia one should consider glucagon'; others reflect the editor's fallibility. Among the usual windmills tilted at are cardiologists, health maintenance organizations, conservative treatment of graft infection, endovascular surgery, the healthcare financing administration and all interventional radiologists. Still in favour are asymptomatic carotid endarterectomy, motherhood and apple pie, and, inevitably, the venous studies laboratory swindle. The selection of papers is generally robust. The large number from Oregon Health Sciences University, Portland, USA perhaps reflects their quality or perhaps not. Any vascular surgeons still worried that they missed something important in the literature last year should buy a copy of this book to be reassured they did not.

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Principles and Practice of Surgical Pathology and Cytopathology

S. G. Silverberg (ed.). 286 × 230 mm (three volumes). Pp. Vol. 1, 1068; Vol. 2, 1157; Vol. 3, 1031. Illustrated. 1997. Edinburgh: Churchill Livingstone. £335.

This ambitious work is an update of an established general pathology text. Although other good surgical pathology tomes are available, this is unique because it integrates cytological and

histopathological diagnosis in one text. This is a laudable goal in that it shifts cytopathology squarely into the ambit of general pathology practice, rather than leaving it out on a limb where it has long been. The unavoidable corollary of this move is a lengthy three-volume work with a price tag significantly higher than that of its peers. The authors have assembled a tremendous amount of information in a rapidly changing field in a palatable fashion without sacrificing the basic core of the subject. The opening chapters dealing with general aspects, such as quality assurance and computerization as well as the role of special techniques in pathology, are particularly comprehensive and topical. The organ-specific chapters are variable in style, reflecting the multi-author contributions, but are well set out and thorough. Although the worth of a book such as this is best assessed through routine use, I am confident that *Principles and Practice of Surgical Pathology and Cytopathology* will occupy a prominent place on the shelf in routine pathology reporting rooms throughout the world.

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ABC of Urology

C. Dawson and H. Whitfield (eds). 296 × 212 mm. Pp. 46. Illustrated. 1997. London: BMJ Publishing Group. £16.

This A4-sized booklet of 46 pages is a collection of articles that first appeared in the pages of the *British Medical Journal*. Written as an introduction to urology for the non-specialist (students, nurses, junior doctors, surgeons in training), it provides an excellent starting point for those who wish to gain a basic understanding of the subject. The 12 chapters cover evaluation of the urological patient, outflow obstruction, urological emergency, incontinence, subfertility and sexual dysfunction, before moving on to urological malignancy, stone disease, paediatric problems and, finally, trauma and reconstruction. The volume is well laid out with colour pictures, figures and boxed tables which highlight key points. It is easy to read and fulfils the authors' aims. My only criticism is that a couple of the photographs have colours that have faded, but I would not let that stop anyone buying a book that provides an excellent introduction to urology.

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Recent Advances in Surgery 20

I. Taylor and C. D. Johnson (eds). 234 × 156 mm. Pp. 294. Illustrated. 1997. Edinburgh: Churchill Livingstone. £30.

This most recent book in the series achieves its purpose of updating the reader; the editors are to be congratulated. The opening chapter on surgical haemostasis is the only one with a series of mis-spellings and, in the endoscopic management of gastrointestinal bleeding, no place is found for histoacryl injection therapy of gastric varices, which is an important new development. The chapter on metabolic response to surgery is very informative and those on gastrointestinal bleeding of obscure origin and pancreatic trauma are equally valuable. There are good illustrations in the informative chapter on local excision of rectal tumour, while emphasis on the pivotal place of early computed tomographic scanning in the assessment of the patient

R. J. Cuschieri

with diverticular disease is a new approach that may require further validation before being generally accepted. The contribution on tissue expanders is certainly intriguing and may have application for repair of abdominal wall hernia, as well as the more obvious plastic surgical utilization. The closing chapter 'What's New in the Journals' is the most ambitious to be topical; it should be kept as a future format because of the extent of coverage that has been achieved.

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Synopsis of General Pathology for Surgeons

D. W. K. Cotton. 215 × 138 mm. Pp. 144. Illustrated. 1997. Oxford: Butterworth-Heinemann. £15.99.

This well written concise text is aimed mainly at those studying for postgraduate examinations in surgery. It covers general pathology topics in a short-note style that is easy to pick up and read at any time. The book gives a broad overview of the subject and is detailed enough to encompass most areas covered by surgical postgraduate examinations. It would need to be supplemented in certain areas if it were the only pathology textbook used, but references to key articles given in the text are useful. Although in some areas pathology is a rapidly changing field, this synopsis gives a good and contemporary, if not always state-of-the-art, view. It would certainly be of interest to hard-working trainees who, by nature, want an easy-to-read, 'all I need to know in 128 A5 pages' book. There are many good pathology textbooks but in an area where it has few direct competitors it fares well. As the author comments, the book would also be of use to practising surgeons who wanted an up-to-date view of general pathology

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Carotid Endarterectomy – A Practical Guide

N. L. Browse, A. O. Mansfield and C. C. R. Bishop (eds). 252 × 193 mm. Pp. 126. Illustrated. 1997. Oxford: Butterworth-Heinemann. £49.50.

The authors have set out to provide a comprehensive practical guide for surgeons undertaking carotid surgery. The title is, however, a misnomer, as only eight pages are devoted to the operative procedure itself. None the less, there are nine other chapters ranging from plaque morphology to trials and selection. In particular there are excellent, if somewhat lengthy, chapters on anaesthesia and computed tomographic angio-imaging. Some duplication exists between other chapters, but the gem of brevity and clarity is the chapter on shunting and patching. More could be made of the current controversy surrounding angioplasty and stenting for carotid disease. The role of thrombolytic therapy in the management of acute neurological deficits after carotid endarterectomy receives no mention. Figures, tables and illustrations are good, but why a whole page in colour should be devoted to two rabbit aortas remains a mystery. I have no doubt that this book will become an excellent primer for those training in carotid surgery and will also serve as a source of quick reference for those with an established carotid practice.

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Notices and announcements

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Information. J. Hill, Department of General and Colorectal Surgery, Central Manchester Healthcare Trust, Oxford Road, Manchester M13 9WL, UK

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Information. O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

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Information. Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998

Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer

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Information. G. Buccheri, Scientific Secretary, Ospedale A. Carle, 1-12100 Roccamare (CN), Italy

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For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol, these statistics should be presented in parentheses after the mean value.

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Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ¹ or ¹⁻³. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number, page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher, year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

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